ACTA PÆDIATRICA

EDITORES:

A. LICHTENSTEIN, STOCKHOLM, A. WALLGREN, STOCKHOLM

REDACTORES:

IN DANIA: BENT ANDERSEN, AARHUS, OLUF ANDERSEN, KØBENHAVN, C. E. BLOCH, KØBENHAVN, P. PLUM, KØBENHAVN. *IN FENNIA:* P. HEINIÖ, HELSINGFORS, V. RANTASALO, HELSINGFORS, C.-E. RÄIHÄ, HELSINGFORS, T. SALMI, ÅBO, ARVO YLPPÖ, HELSINGFORS. *IN HOLLANDIA:* E. GORTER, LEIDEN, CORNELIA DE LANGE, AMSTERDAM, J. VAN LOOKEREN CAMPAGNE, GRONINGEN. *IN NORVEGIA:* LEIF SALOMONSEN, OSLO, L. STOLTENBERG, OSLO, A. SUNDAL, OSLO, KIRSTEN UTHEIM TOVERUD, OSLO. *IN SUECIA:* C. GYLLENSWÄRD, UPPSALA, N. MALMBERG, STOCKHOLM, STURE SIWE, LUND, WILHELM WERNSTEDT, STOCKHOLM, Y. ÅKERRÉN, GÖTEBORG.

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EDITOR PROFESSOR A. LICHTENSTEIN

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The 'ACTA PÆDIATRICA' contain articles relating to pediatrics. These articles are published in English, French or German, according to the wishes of the author. Each number consists of about 6 printed sheets, 4 numbers forming a volume. The numbers will be issued as soon as the articles sent in can be printed. The 'Acta' is open to articles from foreign authors in all countries, if sufficient space can be found for them. Manuscripts are to be sent direct to the Editor, to whom also enquiries about the exchanging of papers are to be directed. The subscription should be forwarded to the Editor. Each volume costs 25 Swedish crowns.

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ACTA PÆDIATRICA

(FROM THE PEDIATRIC CLINIC OF CROWN PRINCESS LOUISA'S CHILDREN'S HOSPITAL, CHIEF: PROFESSOR A. LICHTENSTEIN.)

Micromodification of Van Slyke's Method of Determining the Alkali Reserve by Bicarbonate Titration.

By

TORSTEN JOHNSSON.

Determination of the alkali reserve of the blood, expressed in bicarbonate concentration, has become increasingly indispensable in daily hospital routine as a guide in the therapeutic treatment of different conditions of acidosis in children as well as in adults. The majority of the determinations in question have been made in two ways, either gasometrically (van Slyke, Kirk, Mikaelsen, Faartoft, and others) or titrimetically (van Slyke, Lehman, and others).

Van Slyke's gasometric method is the most exact. Micromethod of obtaining a single determination using 0.1 cc serum and the gasometric method have, moreover, been developed. However, the analysis is slow and requires considerable professional skill. The apparatus is expensive and difficult to obtain at present in Sweden.

Lehman has described a titration method for 0.2—1 cc plasma in which the carbon dioxide is forced out with sulphuric acid in order to be absorbed in barium hydroxide, forming insoluble barium carbonate in the Conway chamber. Afterwards the excess barium monoxide is titrated with hydrochloric acid. Since the samples must stand several hours during the procedure the determination takes some time. When micromodification is used the results are somewhat less exact than with the ordinary method. The sample is taken under paraffin. For finger samples this is a fairly complicated procedure.

The titration method worked out by van Slyke is simple, rapid, and fully satisfactory for routine use. Plasma or serum is saturated with alveolar air in a large separatory funnel. Hydrochloric acid is added in excess and the excess is titrated back with sodium hydroxide to the same degree of acidity which the serum dilution had before the addition of hydrochloric acid, i. e. until the colour matches that of a plasma or serum standard from the same sample. Phenol red is the indicator used. 2 titrations require 2 cc serum and the standard requires 1 cc; in other words, a double determination requires 3 cc. Often, however, it is difficult to obtain such large quantities of blood as 7 to 8 cc from infants and small children by venipuncture, particularly since it may be necessary to make repeated determinations. For this reason the writer has tried to adapt the titration method described above to micro use so that it may be employed for blood quantities 10 times smaller. This makes it possible to make determinations using blood from the finger tip.

Technique of Taking Samples and Analysis for Double Determination and Calculation.

1. 0.8—1 cc of finger or venous blood is taken in small test tubes. The samples should not stand longer than half an hour or so. Centrifuged rapidly 20 min. Pipetted off in a separatory funnel (in horizontal position) which is blown through 6 times with expired air passed through a jar with glass beads to eliminate dampness. The funnel is shaken at least 1 min. with a rotary motion in order to distribute a thin, even layer around the sides.
2. 0.5 cc 0.01 N Hcl (in 0.9 % NaCl, CO_2-free) in each of 2 Ellerman tubes.
3. 10 cc 0.9 % NaCl (CO_2-free) in cylinder. 0.3 cc phenol red (= 6 drops at 0.05 cc) is added with a pipette and mixed.
4. 0.1 cc serum added to each Ellerman tube with HCl. Shaken immediately.
5. To prepare the standard, a drop or so of paraffin is added to a third Ellerman tube over a layer of 0.1 cc serum. 1 cc of

phenol red mixture is added after the pipette has been rinsed a few times with the mixture. It proved advisable to dilute the indicator for the standard in the manner indicated in order to obtain the best and most reliable accord with the macromethod.

6. The tubes with the samples are shaken 1 min. with a rotary motion. The tubes may be corked before they are shaken.
7. 0.5 cc 0,9 % common salt is added to each of the tubes containing samples.
8. 0.4 indicator is added to each sample and mixed.
9. Titration until the colour matches that of the standard with 0.01 N NaOH. The colour should be retained at least 30 sec. (0.5 cc 0.01 N HCl — quantity used 0.01 N NaOH) × 100 millimols bicarbonate per 1.000 cc.

The normal bicarbonate concentration in serum or plasma from venous blood is given by Kirk as 22—30 millimols per 1.000 cc.

After the writer had used the method of procedure described above, a comparison was made between this and van Slyke's original method using the same serum from venous blood. 32 samples were determined. The material could be divided up into values under 20 millimols (pathological values) and values over 20 millimols (normal and somewhat low values). A statistical calculation for the first group gave the following result:

	Macromethod	Micromethod
Mean value	13.0	13.27
Standard deviation	±5.12	±5.25
Standard Error of the mean	±1.42	±1.42
and for the second:		
Mean value	26.16	25.69
Standard deviation	±2.42	±2.29
Standard Error of the mean	±0.31	±0.20

Thus for values under 20 the mean values are virtually identical and the standard deviation alike. Values over 20 gave on the average approximately 0.5 millimol lower values with the micromethod. Further statistical work indicated that this difference is statistically probable.

No satisfactory explanation of why the micromethod gave on the average approximately 0.5 millimol lower values can be given. It may possibly be due to the fact that the samples in question belonged for the most part to the first part of the series and that the experimenter was able in the later determinations, when he had become more experienced, to titrate more accurately.

Since the micromethod is meant to act as a guide in therapeutic treatment, the circumstance that it gives somewhat low values in certain cases is probably of no practical significance.

Subsequently the writer himself made a comparison between venous blood and finger blood serum from the same individual. 16 double determinations with each of the 2 methods gave the following results:

	Macromethod	Micromethod
Mean value	26.6	23.6
Standard deviation	±1.58	±1.59
Standard Error of the mean	±0.40	±0.40

Here a statistically established difference of 3 millimols was obtained, a difference which corresponds to the lower bicarbonate content in arterial blood. The composition of blood obtained by pricking the finger is primarily arterial.

Solutions and Apparatus.

1. Liquid paraffin.
2. 0.01 N HCl in 0.9 % NaCl (CO_2-free).
3. 0.9 % Na Cl (CO_2-free).
4. 0.03 % phenol red (phenol red 0.165 gr, sodium hydroxide 0.01 N 47 cc distilled water 8 cc diluted 1 : 10).
5. 0.01 N Na OH in 0.9 % NaCl (CO_2-free).
6. Cock grease (for the stop-cocks on the separatory funnels and the burette).

1 cc burette graduated in 100ths mounted in a burette bottle with soda-lime lock.

50—150 cc separatory funnels without necks.

Glass jars with glass beads, provided with corks. Through

the corks two right-angled glass tubes, one equipped with rubber tubing.

1 and 0.5 pipettes. 0.1 cc Hagedorn pipettes.

Graduated 10 cc cylinder. Ellerman tubes, possibly corks for the latter.

The funnels, tubes, and cylinders are washed in bichromate-sulphuric acid, carefully rinsed in distilled water, and dried. The pipettes are cleaned with alcohol and ether in the usual way.

Summary.

Description of a micromodification of Van Slyke's method of determining the alkali reserve by bicarbonate titration. This modified method seems to be practical for routine use.

Résumé.

Description d'une micromodification de la méthode de van Slyke pour déterminer les réserves d'alcali au moyen du titrage par le bicarbonate, qui paraît pratiquement utilisable dans le travail de routine.

Zusammenfassung.

Beschreibung einer Mikromodifikation von van Slykes Methode zur Bestimmung der Alkalireserve durch Bikarbonattitrierung, welche für Routinarbeit praktisch anwendbar zu sein scheint.

Resumen.

Se describe una micromodificación del método de van Slyke para la determinación de la reserva de álcali mediante titulación de bicarbonato. Este método modificado es al parecer práctico para uso rutinario.

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INSTITUT FÜR PATHOLOGISCHE ANATOMIE UND HISTOLOGIE DER UNIVERSITÄT GENOVA (DIREKTOR PROF. L. AJELLO.)

Über die Pathologie der Gaucherschen Krankheit im frühen Kindesalter (mit besonderer Berücksichtigung der neurologischen Form).

Von

Dr. **ANTONIO GIAMPALMO.**
Prosektor und Dozent.

In den letzten zwanzig Jahren haben verschiedene, meist anatomisch-klinische Beiträge zeigen können, dass es ausser der bekannten, chronisch verlaufenden Form der Gaucherschen Krankheit (G. K.) beim Erwachsenen und Jugendlichen (oder auch beim älteren Kinde) noch eine dem Kleinkinde eigene, sehr schnell tödlich ausgehende Form gibt, die, was die Schwere des Verlaufes betrifft, der Niemann-Pickschen Krankheit (N. P. K.) parallel zu stellen ist, welche bisher fast ausschliesslich in dieser frühesten Lebensperiode beobachtet werden konnte.

Ich sage »fast ausschliesslich», weil einige kürzlich erschienene Arbeiten (siehe bes. die von A. Dusendschon, 1946) das mögliche Bestehen einer, wenn auch sehr seltenen, Form des Erwachsenen der Phosphatid-Lipoidose mit langsamem, chronischem Verlauf aufzeigen, was von grossem Interesse ist. Es scheint also, dass, so wie für die G. K. eine akute, infauste Form der Kleinkindheit besteht, es für die N. P. K. auch eine chronisch verlaufende Form des Erwachsenen gibt. Die beiden klassischen »primären» Lipoidosen erschienen hiernach in einem neuen, erweiterten klinischen Aspekt, in dem beiden eine akute Verlaufsform des Kindes und eine chronische des Erwachsenen gemeinsam wäre.

Das Studium dieser akuten Verlaufsform der G. K. hat nun pathologisch-anatomische und klinische Besonderheiten derselben zutage gefördert, die ein gut abgrenzbares Krankheitsbild ergeben, welches in verschiedenen der genannten Beiträge eine eingehende Beleuchtung findet.

In Bezug auf erstere möchte ich hier nur hervorheben, dass die ursprüngliche Ansicht von Pick, welcher im Gaucher (von ihm allerdings vorwiegend am Erwachsenen studiert) die Speicherung der Cerebroside für an die blutbildenden Organe (Milz, Lymphknoten, Knochenmark) und an die Leber gebunden hielt (mit Vorkommnis der spezifischen Zellen nur in diesen Organen), wohl mit recht dahingehend abgewandelt ist, dass diese Beschränkung, obwohl sie, bis zu einem gewissen Grade, beim Erwachsenen Gültigkeit hat (Ausnahmen fehlen nicht: siehe den Fall von Merklen), nicht gleichermassen für die frühkindliche Form zutrifft. Für letztere haben zahlreiche Mitteilungen autopsischer Fälle die quasi Ubiquität der Gaucherzellen aufgezeigt, welche sich, da sie reticulo-histiocytären Ursprungs sind, in fast allen Organen bilden können, sei es, dass sie von den Reticulumzellen abstammen (was vorwiegend für die Blutbildungsstätten zutrifft), sei es, dass sie sich von den adventitiellen und periadventitiellen Histiocyten herleiten, was überall der Fall sein kann. Dabei ist natürlich zu beachten, dass, da die blutbildenden Organe bei weitem am reichsten an Zellen des reticulo-histiocytären Systems sind, auch beim kleinen Kinde die Beeinträchtigung derselben — mit Prevalenz des splenomegalischen Bildes — im Vordergrunde des Symptomkomplexes steht. Diese Ubiquität der Gaucherzellen beim Kleinkinde mag eine wesentliche Klärung finden in den wohlbekannten Studien von Lubarsch, welcher seinerzeit die besonders reiche Entwicklung und Aktivität des reticulo-histiocytären Systems in den ersten Zeiten des extrauterinen Lebens hervorhob.

Unter den klinischen Besonderheiten sind vor allen Dingen die folgenden zu nennen:

1) Eine häufige Beteiligung des oberflächlichen Lymphknotensystems an den Veränderungen mit dementsprechender diffuser, oberflächlicher Lymphadenomegalie (welch letztere bisher nur für die N. P. K. anerkannt war, für welche sie sogar zu differentialdiagnostischen Zwecken gebraucht wird: der Vergleich wurde allerdings immer, nicht ganz zutreffenderweise, zwischen der N. P. K. und der Form des Erwachsenen der G. K. gezogen). Diese Beteiligung erfährt ihre Erklärung in der Tatsache, dass das reticulo-histiocytäre System Träger der Krankheit ist; es er-

scheint also verständlich, dass die spezifischen Veränderungen sich überall, sei es auch in unterschiedlichem Ausmasse, finden können, und dass insbesondere kein grundsätzlicher Unterschied besteht zwischen oberflächlichen und tiefen Lymphknoten, da dieses System in beiden gleichermassen vorhanden ist.

2) Das beim kleinen Kinde fast konstante Fehlen der, für die Form des Erwachsenen charakteristischen Pigmentation der Haut, und der Pinguecula.

3) Das, im Gegensatz zu der chronischen Form, häufige Fehlen haemorrhagischer Zustände und einer Piastrinopenie.

4) Ein besonderes, ausserordentlich häufiges, nervöses Syndrom, welches sich bei der akuten, frühkindlichen Form zu den übrigen Symptomen gesellt, und welches, wie die Studien dieser letzten 20 Jahre gezeigt haben, das wichtigste klinische Unterscheidungsmerkmal zwischen dieser und der chronischen Form dargestellt.

Die Kenntnis dieser neurologischen Form der G. K. beim Kleinkinde danken wir Woringer und Oberling. Im Jahre 1927 teilten diese beiden AA., Kliniker der erste, Pathologe der zweite, in einer heute allgemein bekannten Arbeit klinische und anatomisch-pathologische Daten mit, welche vier nacheinander im Säuglingsalter in kachektischem Zustande gestorbene Geschwister betreffen, die alle eine schwere Gauchersche Erkrankung mit einer charakteristischen nervösen Symptomatologie darboten: es handelt sich um jene unglückliche Strasburger Familie, deren Eltern später noch weitere Kinder, ebenfalls im Säuglingsalter, an der gleichen Krankheit zu Grunde gehen sahen.

Nur bei zweien dieser vier Fälle war ein pathologisch-anatomisches Studium möglich; ein fünfter Fall derselben Familie wurde später klinisch von Meyer und wieder von Woringer studiert. In der genannten Arbeit sprachen Die AA. von »Maladie de Gaucher chez le Nourrisson» (wie sie auch als Titel ihrer Mitteilung schrieben), und fügten den eigenen eine kleine Zahl anderer ähnlicher Fälle bei, die sie in der Literatur gefunden hatten, nämlich den Fall von Rusca, den von Gerstl und Kraus, einen Fall von Kohn (der von vielen nachfolgenden AA. wiedergegeben aber niemals bibliographisch spezifiziert wird), den von Nauwerck

und Pick und die beiden Fälle von Reber; zehn also im ganzen, oder besser neun, da der Fall von Kohn, weil im Original unauffindbar, von der Wertung ausgeschlossen werden muss. Im Jahre 1930 veröffentlichte Moncrieff einen Fall, ebenfalls mit nervöser Symptomatologie. Zwei weitere werden von Meyer 1932 und in Italien 1934 von Dessylla—Robles mitgeteilt; Meyer machte in späteren Arbeiten auch eine neue Aufstellung aller Fälle, wobei er schon auf fünfzehn kam. Im Jahre 1936 machten Aballi und Kato gelegentlich des Studiums einer eigenen Beobachtung einen neuen Appell, wobei sie schon auf achtzehn Fälle kamen (einschliesslich des, wie gesagt, nicht auffindbaren von Kohn und desjenigen von Pick—Nauwerk, von dem jedoch etwaige neurologische Daten nicht bekannt sind). Im Jahre 1939 erschien ein wichtiger pathologisch-anatomischer Beitrag von Köhne und 1946 endlich konnte ich nach direkter Überprüfung der gesamten konsultierbaren Kasuistik dreiundzwanzig neurologische Fälle von fünfundzwanzig Gauchererkrankungen, nicht nur des Säuglings, sondern auch des Kleinkindes (mit Tod innerhalb der ersten zwei Lebensjahre), einschliesslich eines eigenen, zusammenstellen. In dieser Arbeit finden sich einige von den voraufgehenden AA. übersehene Fälle, so der italienische von di Guglielmo. Aus meiner Arbeit ging also hervor, dass das nervöse Syndrom bei an Gaucher erkrankten Kindern, ausserordentlich häufig (jedoch nicht konstant) beim Säugling (mit Tod etwa innerhalb des ersten Lebensjahres), manchmal auch jenseits dieser Periode (mit Tod innerhalb der ersten beiden Lebensjahre), auftreten kann. Dadurch wurde die Ansicht, welche das nervöse Syndrom ausschliesslich auf das Säuglingsalter beschränkte, überwunden.

Es ist die Absicht des vorliegenden Beitrages, unter Berücksichtigung der neuesten Mitteilungen, sowie auch jener wenigen anderen, die mir erst jetzt in Italien und in einem kürzlichen Aufenthalte in Stockholm zugänglich waren, das anatomisch-klinische Bild dieser infantilen Form mit nervösem Syndrom, sowie die Entwicklung der diesbezüglichen Doktrine zu überprüfen.

Durch Studium der entsprechenden Originalarbeiten ist es mir gelungen, acht weitere Fälle von infantilem G. K. mit nervöser Symptomatologie zu finden. Es sind dies: der von Nagao

(1935), der von Aballi und Kato (1936) der von De Lange (1939) und, unter den neuesten Beiträgen, der von Ullrich (1942), von Schairer (1942) und von Frisell (1943).

In der Kasuistik dieser Arbeit sind die wenigen nicht neurologischen Fälle der ersten beiden Lebensjahre nicht inbegriffen (Scheffield, Graham und Blacklock, Schuster, Paschin und Kritsch Donovan, Espersen), ebenso nicht der Fall von Pick—Nauwerk, von welchem eine etwaige nervöse Symptomatologie nicht bekannt ist, der von di Guglielmo und die beiden von Amato, bei denen die nervösen Symptome so gering sind, dass sie praktisch als nicht vorhanden angesehen werden müssen. Nicht inbegriffen ist auch der Fall von Lindau, von welchem — nach der Symptomatologie, und ganz besonders nach den wiedergegebenen Mikrofotos zu urteilen (in der Abb. Nr. 2, die die Milz betrifft, erscheinen die rundlichen Zellen mit alveolärem Bau mit denen von Pick in der feinvacuolären Phase identisch zu sein) — die Zugehörigkeit zur G. K. bezweifelt werden muss, der von Winter, vom A. als Fall von N. P.scher Krankheit veröffentlicht (als solcher findet er sich auch in meiner Monographie über Speicherkrankheiten von 1947 im Archivio Maragliano di Patologia e Clinica), aber von einigen AA. (Aballi und Kato, De Lange, Frisell) unter die Fälle von G. K. eingereiht, und dann endlich der Phantomfall von Kohn.

Im ganzen sind dreiundvierzig die mir bekannten Fälle einer sicheren G. K. mit Tod innerhalb der ersten beiden Lebensjahre, einschliesslich zweier weiterer Beobachtungen von Frola (aus der Paediatrischen Klinik der Universität Bari — die Mitteilung wurde dem A. persönlich gemacht; die Arbeit über die beiden Fälle ist im Druck). Von diesen 43 Fällen wiesen nicht weniger als 29, also etwa 3/4 der Gesamtzahl, eine nervöse Symptomatologie, wenn allerdings auch in verschiedenem Ausmasse, auf, wie dies aus der beigefügten Tabelle ersichtlich ist. Zu diesen Fällen kommt als dreissigster derjenige eines kleinen Bruders des von mir studierten Kindes, welchen ich retrospektiv, mittels einer exakten Anamnese (die mir aber erst nach Ende des Krieges durch Auffinden der Eltern möglich war) als dieser Gruppe zugehörig erkennen konnte.

Auf Grund der Studien von Oberling und Woringer und der nachfolgenden AA. kann man wohl das wesentliche Bild dieser Krankheit wie folgt definieren:

Es handelt sich in der Mehrzahl der Fälle um Säuglinge des ersten, in geringerer Zahl auch um solche des zweiten Lebenshalbjahres oder solche, die seit kurzem das erste Lebensjahr überschritten haben, bei welchen sich, nach Auftreten einer Splenomegalie (am Anfang ist die Hepatomegalie weniger konstant und auf jeden Fall geringeren Grades und später auftretend als die Milzvergrösserung) in den ersten Wochen oder Monaten oder auch nach den ersten 6 Monaten, oft begleitet von einer leichten Anaemie, eine Hypertonie der Muskulatur entwickelt, welche oft von hypotonischen Perioden unterbrochen oder sogar eingeleitet wird. Gleichzeitig wird ein Stillstand der geistigen Entwicklung erkennbar und der Hypertonus, der fast immer von Opisthotonus mit Nackensteife und Trisma begleitet ist, nimmt langsam an Intensität zu. Die Gliedmassen nehmen mit der Zeit eine Beugestellung ein, die ausgesprochene Tendenz hat, sich zu stabilisieren, bis zur Erreichung, in manchen Fällen, einer echten Kontraktur, wobei jedoch die passive Beweglichkeit immer erhalten bleibt (die Arme neigen, wie von manchen AA. hervorgehoben wird, dazu, sich mit geballten Fäusten vor das Gesicht zu beugen oder werden sogar bis in den Mund gebracht); gewöhnlich tritt auch schon frühzeitig ein Strabismus convergens auf, zuerst nur vorübergehend, dann permanent, welcher sehr charakteristisch ist (der Augenarzt Nordmann hat auf dieses Zeichen die besondere Aufmerksamkeit gelenkt).

Bei der klinischen Untersuchung besteht fast konstant Sehnen-Hyperreflexie, unter Umständen mit polykinetischer Reaktion (selten auch Hyporeflexie). Kernig und Brudzinski sind manchmal positiv und können, wegen der meist gleichzeitig vorhandenen Nackensteife zu der fälschlichen Diagnose einer Meningitis führen, welche jedoch durch den vollkommen negativen Liquorbefund ausgeschlossen werden kann. Manchmal besteht Babinski (aber auch diesem Symptom darf keine grosse Bedeutung beigemessen werden, da es schon häufig normalerweise beim Säugling vorhanden ist). Im Verlaufe der Krankheit verfallen die Kinder

immer mehr, ihre körperliche Entwicklung steht still und die psychischen Störungen treten deutlicher hervor durch einen zunehmend apathischen Zustand mit gänzlicher Uninteressiertheit an der Umwelt. Dieses psychische Defizit ist von einer steigenden Bewegungsarmut der Gesichtsmimik und der Glieder begleitet, welche jetzt fast immer gebeugt gehalten werden und sich in einem dauernden Starrezustande befinden. Zu einem variierenden Zeitpunkte, oft sehr frühzeitig, oft auch erst im Anschluss an das Erscheinen der nervösen Symptome, treten sehr häufig Störungen von Seiten des vegetativen Nervensystems zutage: oft bestehen laryngospastische Krisen mit spastischem Husten (die Verwechselung mit Pertussis ist möglich!) sowie dyspnoische und apnoische Anfälle, welche meist von Cyanose begleitet sind; häufig besteht Dysphagie, seltener Erbrechen und anfallsartiges Schwitzen. Zu diesen neurovegetativen Störungen gesellen sich häufig unregelmässige Temperatursteigerungen, sine materia, d. h., wenigstens nicht durch nachweisbare entzündliche Veränderungen hervorgerufen.

Mit der beschriebenen Symptomatologie, die immer ausgeprägter zur Entwicklung kommt, gerät das Kind langsam in einen schweren, hypotrophischen und endlich kachektischen Zustand, während die schnell wachsende psychische Involution häufig den Grad einer Idiotie erreicht (eine Untersuchung des Augenhintergrundes zeitigt jedoch keine Veränderungen, wie sie dagegen bei der amaurotischen Idiotie und bei den idiotischen Formen der N. P. K. zu finden sind). Zu diesem Zeitpunkt kommt es, wenn nicht eine intercurrierende Krankheit, meist eine Bronchopneumonie, den Verlauf bereits abgekürzt hat, unausweichlich zum tödlichen Ende. Der Verlauf ist im allgemeinen akuter und schwerer (und regelmässiger und reicher mit einer nervösen Symptomatologie versehen) bei den Fällen mit sichtbarem Beginn in den ersten Lebensmonaten und mit Exitus innerhalb des ersten Jahres; er ist dagegen weniger akut und weniger konstant von nervösen Symptomen, welche meist auch nicht so reichhaltig sind, begleitet bei jenen Fällen, bei denen die Krankheit scheinbar erst nach dem ersten Lebenshalbjahre ihren Anfang nimmt, mit Tod innerhalb des zweiten Lebensjahres.

Aus der oben gemachten Krankheitsbeschreibung (welche auf einer analytischen Überprüfung der gesamten Kasuistik basiert) geht klar hervor, dass, obwohl die schwerste und am ausgesprochensten neurologische Form diejenige mit Tod im Säuglingsalter ist (allerdings fehlen aber auch in diesem Alter nicht einige wenige, neurologisch stumme Fälle — siehe die beiden Fälle, Brüder, von Frola und den kürzlich erschienenen Fall von Espersen), so gibt es dennoch Beobachtungen (ich verweise diesbezüglich auch auf die angefügte Tabelle), bei welchen ein nervöses Syndrom jenseits des ersten Lebensjahres auftrat. Der Unterschied liegt hauptsächlich in der verschiedenen Schnelligkeit und Schwere des Verlaufs. Oberling und Woringer sprachen von einer Form der Gaucher-Krankheit beim Säugling und hoben besonders das nervöse Syndrom hervor; Rowland prägte 1936 dafür die Bezeichnung »Akute» G. K.; De Lange zog 1939 die Definition »maligne Form» der G. K. vor; ich selbst wählte in meiner 1946 im Policlinico Infantile erschienenen Arbeit die Denomination »frühkindliche Form der G. K.», da ich gesehen hatte, dass die neurologische Form nicht nur im ersten Lebenshalbjahr, sondern auch nach diesem Zeitpunkte, ja sogar, wenn auch seltener, nach dem ersten Lebensjahre (mit Tod innerhalb des zweiten Lebensjahres) auftreten kann. In der Arbeit von Frisell von 1943, schlägt dieser A. auf Grund des allgemeinen klinischen Verlaufes vor, ausser der akuten Form des Säuglings noch eine subakute Form der Frühkindheit zu unterscheiden, deren Beginn in eine nach den ersten sechs Lebensmonaten liegende Periode fällt. Dieser Vorschlag erscheint mir zweckmässig, da man tatsächlich, wie wir gesehen haben, bei der frühkindlichen G. K. die akuten Formen mit Beginn im ersten Lebenshalbjahre von jenen subakuten, wenn auch gleichfalls fatalen, mit späterem Beginn deutlich unterscheiden kann.

Oberling und Woringer ordnen die beschriebene nervöse Symptomatologie unter die Syndrome von pyramidalem Typ ein; sehr wahrscheinlich wurden sie hierzu unter anderem auch durch die Befunde bei ihren beiden autopsischen Fällen veranlasst, bei welchen sie degenerative Veränderungen nur in den Nervenzellen der Rinde gefunden hatten (auf diese Frage komme ich noch bei Besprechung der pathologischen Anatomie zurück), welche

von ihnen als »progressive Rindenatrophie« bezeichnet wurde. Die beiden AA. verglichen das beobachtete Syndrom mit dem der entrindeten Starre. Meyer dagegen glaubt in seiner Arbeit, diese Form als den Syndromen vom pseudobulbären Typ zugehörig ansprechen zu müssen. Tatsächlich hat das Syndrom, wie die Klinik der verschiedenen Fälle zu zeigen scheint, und wie es auch wohl von den, leider noch sehr wenig zahlreichen, histologischen Befunden am Nervensystem bestätigt wird, nicht ausschliesslich pyramidalen und neurovegetativen, sondern auch extrapyramidalen Charakter, was ich in meiner voraufgehenden Arbeit hervorgehoben habe. Die gleiche Ansicht wird von De Lange schon 1939 zum Ausdruck gebracht. Wahrhaftig kann man einigen Symptomen — der Hypertonie fast stets ohne pathologische Reflexe, der Armut an Mimik und Bewegungen, dem katatonischen Zustande — einen überzeugenden extrapyramidalen Charakter nicht absprechen. Dementsprechend zeigen, wie man sehen wird, die histopathologischen Befunde von Köhne, von Schairer und meine eigenen, eine Diffusion der Veränderungen der Nervenzellen nicht nur in der Rinde und in den Basalganglien sondern manchmal auch im Kleinhirn.

Eine aufmerksame Prüfung der von den verschiedenen AA. mitgeteilten histopathologischen Befunde erscheint ganz besonders wichtig mit Hinblick auf die noch nicht ganz klare Pathogenese der nervösen Veränderungen und die mit denselben zusammenhängende Symptomatologie. Schon in der Arbeit von Rusca aus dem Jahre 1921 findet sich der erste Hinweis auf Veränderungen in der nervösen Substanz: dieser A. berichtet, im Gehirn Atrophie und Verringerung der Zahl der Pyramidenzellen gefunden zu haben. In der Doktordissertation von Jenny (Basel 1930) ist gesagt (bei De Lange wiedergegeben), dass bei dem zweiten Falle von Reber (1924) Ödem der Hirnrinde und schwere Degeneration der Ganglienzellen, welche teilweise bis zu völliger Zerstörung derselben reichte, vorhanden gewesen seien. Im Jahre 1927 endlich erscheint die Monographie von Oberling und Woringer. Aus dieser geht hervor, dass in ihren beiden durch Sektion kontrollierten Fällen bei Untersuchung des Gehirns die Rindenzellen den Zustand der chronischen Zellerkrankung von Nissl (einfache

Schrumpfung von Spielmeyer), sowie zum Teil ausserdem Tigrolyse und Vakuolisation im Zellkörper und in den Fortsätzen aufwiesen; es bestand ausserdem Proliferation der gliösen Trabantzellen: der genannte Befund war sehr ausgesprochen im ersten der beiden Fälle (dem zweiten der vier von den AA. beobachteten), einem mit 5 Monaten gestorbenen Säugling; er war weniger entwickelt im zweiten Falle (dem vierten der vier Fälle), einem Säugling, der schon nach einem Monat starb, als die nervösen Symptome eben erst anfingen, sich bemerkbar zu machen. Der Pathologe Oberling beschreibt die in den beiden autopsischen Fällen zur Beobachtung gekommenen Veränderungen an der nervösen Substanz als »progressive Rindenatrophie»; der Kliniker Woringer definiert in der gemeinsamen Arbeit den zugehörigen nervösen Symptomkomplex als »Syndrome de décortication progressive et finalement complète». Die Tatsache, bei ihren Fällen nur Rindenläsionen gefunden zu haben, veranlasste die beiden Forscher, in diesem von ihnen zum ersten Male isolierten Syndrom nur rein pyramidale Züge zu erblicken.

Hamperl 1929 tut den bei seinem Falle angetroffenen nervösen Veränderungen, welche übrigens lediglich in einer leichten Homogenisierung der Ganglienzellen der Hirnrinde bestanden, nur oberflächliche Erwähnung. Es ist Köhne, der 1939 in seiner speziell auf die Läsionen des Zentralnervensystems gerichteten Studie zum ersten Male hervorhebt, dass bei seinem Falle nicht nur die Nervenzellen der Rinde, sondern auch die vieler anderer Sektoren und ganz besonders die der zentralen Ganglien schwer verändert seien. Auch er beschreibt an den Nervenzellen im Wesentlichen regressive Veränderungen vom Typ der chronischen Zellerkrankung von Nissl, sowie mässige reaktive Gliose. Unter Betonung der Tatsache, dass Degenerationserscheinungen sich, wenn auch in verschiedenem Ausmasse, überall im Gehirn finden, weist er darauf hin, dass dieselben keinen besonderen und spezifischen Charakter haben, sondern dass es sich um regressive Prozesse handele, wie sie in vielen anderen akuten und chronischen Erkrankungen des Nervensystems anzutreffen seien. Auch Schairer beschreibt 1942 bei seinem Falle diffuse Veränderungen vom Typus der schweren Zellerkrankung von Nissl und vom sklero-

tischen Typ. Diese Veränderungen erscheinen geringgradig in der Rinde, ausgesprochener dagegen in den Zentralganglien, in der Brücke, in der Uliva und im Nucleus dentatus; auch die Purkinje-Zellen befinden sich in einem mässigen Schrumpfungszustande. Auch in diesem Falle besteht ein gewisser Grad glialer Reaktion. Schairer hebt ebenfalls den unspezifischen Charakter der Alterationen hervor, die ja auch in der Histopathologie des Nervensystems wohl bekannt sind. Er weist jedoch darauf hin, dass er in einigen Nervenzellen der Zentralganglien deutliche Zeichen einer Speicherung (mit Verlagerung des Kernes an die Peripherie), erkennbar an dem Vorhandensein grosser Vacuolen und kleiner Partikel einer granulösen Substanz, welche sich beim Färben genau wie jene in den Gaucherzellen verhielt, gefunden habe. Dieser Fall von Schairer ist der dritte (die ersten beiden sind die von Oberling und Woringer), in welchem einige Nervenzellen ausser den mehr oder weniger ausgesprochenen Schrumpfungsprozessen auch vacuoläre Bildungen aufwiesen. Wie schon einleitend gesagt, berücksichtige ich den Fall von Lindau, von dem ebenfalls die histopathologischen Befunde des Nervensystems vorliegen, nicht, da seine Zugehörigkeit zur frühkindlichen G. K. nicht als sicher angesehen werden kann. Im Jahre 1945 endlich habe ich selbst die histopathologischen Befunde am Nervensystem bei meinem Falle mitgeteilt: auch ich fand in der Rinde, noch mehr aber in den Basalganglien, regressive Veränderungen von dem gleichen, bereits beschriebenen Typ, so wie ich auch progressive und regressive Prozesse an der Glia beobachten konnte. Ich schloss deshalb, auch auf Grund der wenigen vorhergehenden Mitteilungen, und im Einklang mit Köhne, dass bei der G. K. mit nervöser Symptomatologie die Läsionen nicht notwendigerweise auf die Rinde begrenzt sein müssen, wie dies ursprünglich von Oberling und Woringer beschrieben war. Die Ausbreitung des Prozesses erklärt meines Erachtens vor allem auch sehr gut die Reichhaltigkeit der Befunde des neurologischen Symptombildes, in welchem ich, wie schon gesagt, auch eine extrapyramidale Physiognomie erblicke.

Auf Grund dieser, wenn auch nicht sehr zahlreichen, histopathologischen Befunde am Zentralnervensystem, und auf Grund

der schon grösseren Zahl der sehr dettagliierten Krankengeschichten, erscheint es wohl ziemlich klar, dass die neurologische Form der kindlichen G. K. nicht, wie deren erste Beschreiber (Woringer und Oberling) auf Grund der geringen initialen Statistik angenommen hatten, lediglich auf das Säuglingsalter beschränkt ist, und dass auch der Sitz der Veränderungen nicht auf die Hirnrinde begrenzt ist, sondern sich auf alle neuronalen Gebiete, und insbesondere auf die Basalganglien erstreckt, und dass infolgedessen die nervöse Symptomatologie nicht ausschliesslich pyramidalen Charakter trägt, sondern auch reichhaltiger, und auf jeden Fall mit unzweifelhaft extrapyramidalen Zügen ausgestattet erscheinen kann.

Für eine diskriminierende, exakte Analyse der verschiedenen nervösen Symptome bin ich nicht zuständig. Diese könnte Aufgabe einer von Neurologen gemachten Studie sein; mir liegt vorerst nur daran, hervorzuheben, dass die nervöse Form der G. K. sich auf das ganze frühkindliche Alter erstrecken kann, und dass der Reichhaltigkeit der bei den klinischen Fällen beobachteten nervösen Symptomatologie in den wenigen, histopathologisch untersuchten Fällen eine entsprechende Ausbreitung der Veränderungen an den Nervenzellen über das ganze Gehirn parallel zu setzen ist. Was die allgemeinen Probleme der Pathogenese der G. K. sowie der frühkindlichen Form derselben anbetrifft, so verweise ich auf meine schon zitierten Arbeiten. Hier dagegen möchte ich bei der pathogenetischen Deutung der Befunde am Zentralnervensystem verweilen.

Am Schlusse meiner Arbeit im Policlinico Infantile 1946 gab ich der Ansicht Ausdruck, dass, um einen besseren Einblick in die Zusammenhänge der Pathogenese dieser Krankheit zu gewinnen, es nötig sei, sich einige Tatsachen gut zu vergegenwärtigen, nämlich:

1) dass beim älteren Kinde, beim Jugendlichen und beim Erwachsenen die neurologische Form fast nie zu beobachten ist;

Als seltene Ausnahmen von dieser Regel sind zu nennen:

Der Fall von Evans, bei welchem die Krankheit mit zwei Jahren beginnt, und bei dem mit 3 $^1/_2$ Jahren zuerst partielle und dann generali-

sierte Krampfanfälle auftreten; Tod mit 5 Jahren (Autopsie). *Die ersten zwei Fälle von Reiss und Kato*: I, japanisches Kind, zuerst untersucht im Alter von 3 Jahren, mit Spleno-Hepatomegalie und Unfähigkeit zu laufen; nach und nach treten Hyperreflexie, Parese des N. Abducens, Schwächung des Visus und Hypertonie mit Opisthotonus auf, die allmählich immer stärker werden; mit 4 Jahren Tachypnoe und Stridor respiratorius; Splenektomie; progressive Verschlechterung mit Anaemie, häufigen Bronchopneumonien, haemorragischen Erscheinungen, Knochenveränderungen und generalisierten Krampfanfällen. Tod mit 7 Jahren in einem Zustande permanenter Starre. II, Bruder des vorhergehenden, zuerst untersucht im Alter von 3 Jahren: Splenomegalie, Unfähigkeit, zu laufen, leichte Abducensparese, Schwächung des Visus, ausgesprochene Hyperreflexie; Neigung zu Kernig, Klonus des Fusses; profuse Schweissausbrüche, Somnolenz; Splenectomie; progressive Verschlechterung mit generalisierter Hypertonie; Zunahme von Strabismus und Krampfanfällen; Tod mit 6 Jahren. Die AA. berichten noch von einem dritten Bruder, im Alter von 15 Monaten untersucht, der ebenfalls an Gaucher erkrankt war und nicht laufen konnte; Tod mit 2 Jahren (dieser letzte Fall ist in der beigefügten Tabelle nicht geführt, weil zu spärlich mit Daten versehen). *Der Fall von af Klercker*, ein Kind, das mit 3 Jahren in Spitalspflege kam und bei dem eine G. K. mit schweren Knochenveränderungen diagnostiziert wurde (die einige Monate später ausgeführte Splenektomie bestätigte diese Diagnose). Die Krankengeschichte erwähnt Temperatursteigerungen sine Materia, profuse Schweisse und häufige Anfälle eines spastischen Hustens. *Der Fall von Meyers*, ein Kind mit Splenomegalie schon in den ersten Lebensmonaten, bei dem sich die Krankheit trotz Splenektomie mit 3 Jahren weiter entwickelte unter besonderer Beteiligung des Skelettes (osteopathische Form der G. K.) und der Lungen; mit 7 Jahren nervöse Erscheinungen vorwiegend spastischer Natur, denen bald der Tod folgte (Obduktion, jedoch ohne Hirnsektion). Ausser diesen, immer noch im Kindesalter sich abspielenden Fällen gibt es *eine Beobachtung von Van Bogaert* bei einem Erwachsenen, der ein Reynaud-artiges Syndrom, Pigmentation der Haut und extrapyramidale Steife der unteren Extremitäten aufwies (klinischer Fall).

2) dass die im Zentralnervensystem angetroffenen degenerativen Veränderungen der Neurone keinen spezifischen Charakter haben und jedenfalls nicht von einer Cerebrosid-Speicherung herzurühren scheinen.

3) dass die nervöse Symptomatologie um so schwerer ist, je früher die Krankheit, oder besser gesagt, die klinische Manifestation derselben, beginnt.

Mit grosser Wahrscheinlichkeit wird man deshalb eine enge Beziehung zwischen dem Krankheitsprozess im Zentralnervensystem und der Entwicklung desselben, insbesondere seiner Reifung, annehmen müssen, welche bekanntlich auch nach der Geburt, speziell, was die Bildung der Myelinscheiden anbetrifft, fortschreitet. Nun scheint es, auf Grund der Untersuchungen von Tropp, dass die Substanzen, von welchen das Cerasin durch Vereinigung mit Galaktose seinen Ursprung nimmt (vorwiegend Lignocerilsfingosin), physiologisch in den an reticulo-histiocytären Zellen besonders reichen Organen gebildet werden (siehe auch Thannhauser–Franck–Bielschowsky), wie besonders Milz, Lymphknoten, Leber und Lunge. Tropp glaubt auch, dass das ins Gehirn gelangte Cerasin sich physiologisch in Loco in die anderen Cerebroside (Cerebron, Nervon, Oxynervon) differenziere, welche, obwohl sie im Gehirn zu finden sind, niemals an der Peripherie angetroffen werden. Von diesen Voraussetzungen ausgehend, waren nun er und Eppinger die ersten, welche vermuteten, dass die neurologische Form der G. K. im frühen Kindesalter von der nicht erfolgten Bereitstellung der erforderlichen Lipoide, insbesondere des Cerasins, für das Zentralnervensystem des Säuglings abhängen könne. Diese Ansicht scheint auch eine weitere Bestätigung in der Tatsache zu finden, dass beim Erwachsenen, bei dem die Struktur des Nervensystems schon völlig ausgebildet ist, und dementsprechend die Notwendigkeit, dasselbe mit Cerebrosiden zu versorgen, nicht mehr, oder nur noch in ganz geringem Umfange besteht, das nervöse Syndrom nicht anzutreffen ist. Nach Tropp, Thompson und Payiling könnte die nicht erfolgte Versorgung des Gehirns mit Cerasin damit zusammenhängen, dass diese Substanz sich infolge des dystrophischen Prozesses, von dem die histiocytären Zellen befallen sind, in eben diesen Zellen anhäuft und nicht nach aussen abgegeben wird (»Lipoidsperre» von Tropp). Danach würde es sich bei der nervösen Form der G. K. um eine grundsätzlich andere Situation handeln, als sie bei der nervösen Form der N. P.schen Krankheit vorliegt. Wie ich in meiner Monographie hervorhob, bestehen bei letzterer die Veränderungen in Lipoidspeicherung (Phosphatide: Sphingomyelin), während diese bei der nervösen Form der G. K. durch Lipoidmangel (Cerebro-

side: Cerasin) hervorgerufen sein könnten. Ich sagte weiter, dass die »Lipoidsperre» in den reticulohistiocytären Zellen, welche die Ursache dieser Karenz zu sein scheint, auch von der bekannten Hydrophobie der Cerebroside abhängen könne, welche bewirkt, dass die Gaucherzellen nicht, entsprechend den Vorgängen in den Pickzellen (welche hydrophile Phosphatide enthalten) einer raschen Disgregation unterliegen, sondern im allgemeinen homogen und kompakt bleiben, auch wenn sie der Nekrose anheimfallen. Während also bei der N. P. K. die schnelle und ausgebreitete »schaumige Auflösung» der Pickzellen eine Überschwemmung des Kreislaufes mit den Detritusmassen derselben und entsprechende sekundäre Veränderungen durch Zufuhr hervorruft, ist dies nicht der Fall bei der G. K. Zur Demonstration dieses verschiedenartigen Verhaltens wies ich darauf hin, dass bei der N. P. K. (wie ich auf Grund einer eigenen Beobachtung, und auf Grund des Studiums der Fälle der Literatur feststellen konnte) die zugehörigen Lymphknoten der schwer betroffenen Organe (so z. B. die des Milzhilus) im Vergleich mit den übrigen Lymphknoten sehr viel stärker verändert sind, und zwar, weil bei ihnen zu der, durch die ursprüngliche Zelldystrophie verursachten Speicherung, mit aller Wahrscheinlichkeit noch diejenige durch Zufuhr von Phosphatidmaterial hinzukommt, und dass die Leber auch im Parenchym stark verändert ist, weil sich in diesem Organe ebenfalls, durch Zufuhr von Phosphatiden der Milz über die V. Splenica und V. Porta, diffuse mesenchymale und parenchymale Veränderungen noch zu der primären Dystrophie seiner histiocytären Elemente hinzugesellen; bei der G. K. dagegen finden sich derartige Unterschiede bezüglich der Beeinträchtigung der Lymphknoten gar nicht oder nur eben angedeutet, und entsprechend fehlt die schwere Leberveränderung, ja, die Beteiligung des Organs ist im allgemeinen geringgradig und auf die Zellen mesenchymalen Ursprungs begrenzt.

Dieser Versuch, etwas Licht in die Pathogenese der nervösen Form der G. K. zu bringen, wird integriert und teilweise modifiziert durch die Schlussfolgerungen, die Schairer aus seinen histologischen Befunden zieht. Dieser A. fand, wie schon voraufgehend

gesagt, in seinem Falle, ebenso wie Oberling in seinen beiden autopsischen Fällen, ausser den predominierenden sklerotischen Veränderungen der Nervenzellen auch vereinzelt solche mit Vacuolenbildungen, welche Granula einer Substanz enthielten, die histochemisch jener in den typischen Gaucherzellen gespeicherten ähnlich war. Schairer neigt auf Grund dieser Befunde dazu, die nicht erfolgte Belieferung des Gehirns mit Cerasin als Ursache der Veränderungen desselben bei der neurologischen Form der kindlichen G. K. abzulehnen und scheint vielmehr annehmen zu wollen, dass es sich auch im Gehirn um eine primäre Zelldystrophie handele. Andererseits betont er, wie aus dem Studium der Literatur hervorgehe, dass die Cerebroside hauptsächlich beim Aufbau der Markscheiden Verwendung fänden, während sich in den Ganglienzellen (deren Alterationen das histopathologische Bild beherrschen) vorwiegend andere Lipoide, die Ganglioside, eine chemisch den Cerebrosiden verwandte Substanz, welche durch Hinzufügung von Zucker und Neuroaminsäure aus diesen entstehen kann, fänden. Nach Schairer wäre deshalb daran zu denken, dass die Störung des Zellstoffwechsels sich auch auf die Ganglioside erstrecke, deren Bildung in irgendeiner Weise beeinträchtigt sei. Es sei folglich das Fehlen derselben die Hauptursache der Degeneration der Ganglienzellen, während die in einigen Nervenzellen beobachtete, gespeicherte Substanz Cerasin sein könne, dessen anschliessende Verwandlung in Ganglioside nicht erfolgen konnte.

Aus dem Gesagten geht hervor, dass das Problem der Pathogenese der nervösen Veränderungen trotz einschlägiger Studien noch nicht als gelöst betrachtet werden kann; es ist möglich, dass die z. T. auf Tatsachen fussenden mitgeteilten Hypothesen der Wahrheit recht nahe kommen; aber darüber lässt sich vorerst nichts Abschliessendes sagen; andererseits sind es auch noch zu wenige Fälle, in denen das Nervensystem histologisch und besonders histochemisch untersucht wurde. Von neuen, exakt ausgewerteten Beobachtungen wird man auch in diesem Sinne weitere Klärungen erwarten dürfen.

Abb. 1. Typische hypertonische Haltung mit gebeugten Armen bei einem Falle von Gaucherkrankheit der frühen Kindheit. Man beachte auch den Strabismus convergens (Beobachtung Aballi und Kato).

Abb. 2. Typische Amimie des Gesichtes mit Strabismus bei einem anderen Falle von Gaucherkrankheit des frühen Kindesalters (Beobachtung Meyer).

Abb. 3. Die beiden unterentwickelten, splenomegalischen und mongoloiden Geschwister der Fälle 29 und 30 der Kasuistik (Beobachtung Giampalmo).

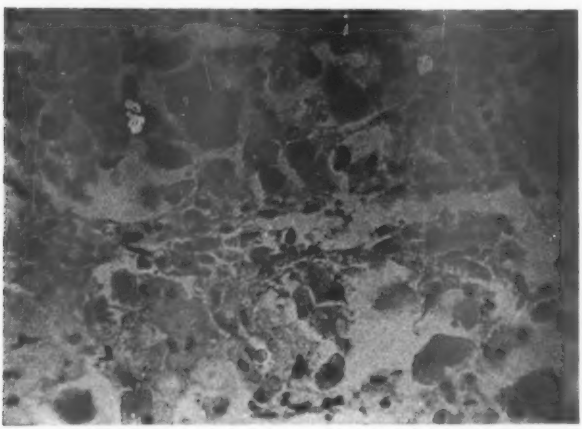

Abb. 4. Gaucherzellen in der Milz; mittlere Vergrösserung (Beobachtung Giampalmo).

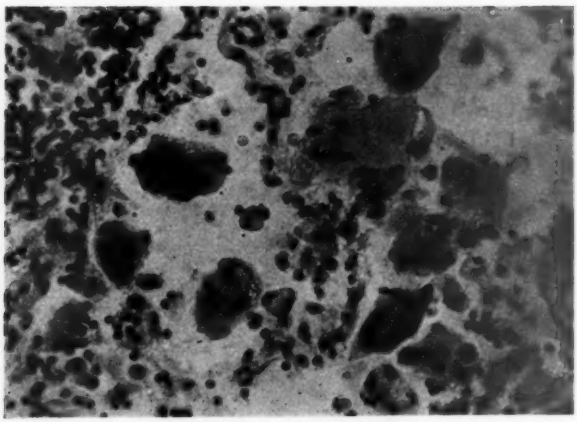

Abb. 5. Polynucleäre Gaucherzellen in einem Lymphknoten; mittlere Vergrösserung (Beobachtung Giampalmo).

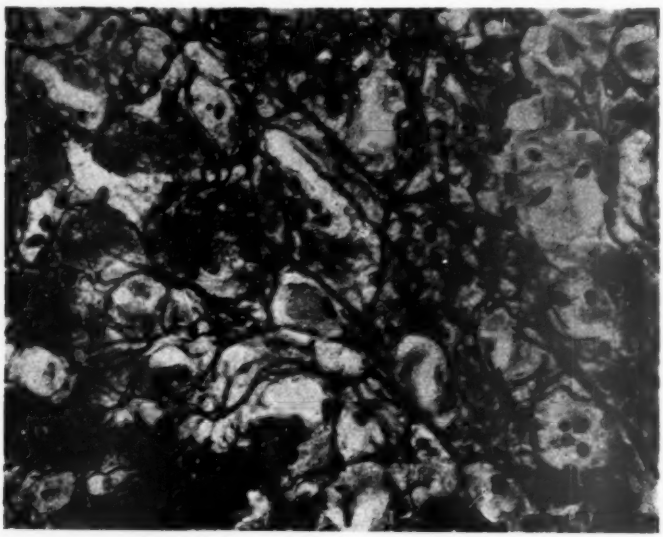

Abb. 6. Innere Zone eines Leberläppchens (Färbung Bielschowsky-Maresch) bei mittlerer Vergrösserung. Rechts und in der Mitte zahlreiche Gaucherzellen (die hellen) zwischen den Leberbälkchen (dunkle Zellen) (Beobachtung Giampalmo).

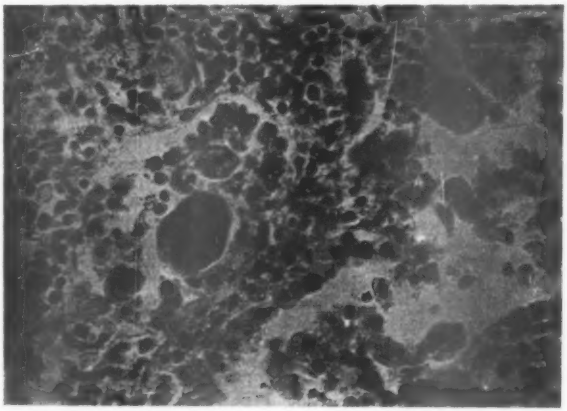

Abb. 7. Gaucherzellen in den Lungenalveolen; mittlere Vergrösserung (Beobachtung Giampalmo).

Abb. 8. Atrophie und »Sklerose» der Nervenzellen im Nucleus Caudatus; mittlere Vergrösserung (Beobachtung Giampalmo).

Klinische und pathologisch-anatomische Daten der Fälle von Gaucher- (Akute und

(Von allen wiedergegebenen Fällen sind die Angab[illegible]n

Nr	Autor	Geschlecht und Alter zu Beginn der Krankheit	Die wichtigsten klinischen Daten und die nervöse Symptomatologie
1	Rusca 1921	♂, 6 Monate	Rachitismus; hypochrome Anaemie; bräunliche Haut; ausgesprochene Hepato-Splenomegalie. *Nackensteife; Kontraktur der Gliedmassen in Beugestellung; Strabismus internus links; Trisma; Laryngospasmus und spastischer Husten;* Gaucherzellen im Milzpunktat. Fortschreitender Verfall; Tod in kachektischem Zustande.
2	Gerstl Kraus 1921	♀, 6 Monate	Frühgeburt; rachitischer Zwergwuchs; Dreizackhand beiderseits; Hernia inguinalis beiderseits; chronische Enteritis; Splenomegalie; *geistige Entwicklung zurückgeblieben; Hypertonie; Strabismus convergens; respiratorischer Stridor.* Fortschreitender Verfall. Tod durch Bronchopneumonie.
3	Reber 1924 (I)	♂, 6 Monate	Bruder des folgenden: Spleno-Hepatomegalie; Anaemie; *Nackensteife; Hypertonie; Steigerung der Tiefenreflexe; Dysphagie; Temperatursteigerungen.* Tod durch fortschreitenden Verfall.
4	Reber 1924 (II)	♀, 5 Monate	Schwester des vorhergehenden; Spleno-Hepatomegalie; Anaemie. *Nackensteife; Hypertonie; Steigerung der Tiefenreflexe; spasmodischer Husten; Temperatursteigerungen.* Tod durch fortschreitenden Verfall.
5	Oberling Woringer 1927 (I)	♂, 5 Monate	Erstes von 4 befallenen Geschwistern. Anamnestisch diagnostizierter Fall. *Stillstand der geistigen Entwicklung; Apathie; Opisthotonus; Strabismus convergens; Dysphagie; Krampfanfälle mit Erstickungssymptomen und Cyanose.* Tod während eines dieser Anfälle.
6	Oberling Woringer 1927 (II)	♀, 5 Monate	Zweites der vier befallenen Geschwister. Spleno-Hepatomegalie; Vergrösserung der obeflächlichen Lymphknoten; leichte Anaemie; Abmagerung. *Stillstand der psychischen Entwicklung; Hypertonie; Opisthotonus; Strabismus convergens; Sehnenreflexe gesteigert und polykinetisch; Trisma; Dysphagie; Erstickungsanfälle; Stridor respiratorius; Temperatursteigerungen.* Tod in kachektischem Zustande durch Bronchopneumonie.

krankheit im frühen Kindesalter mit nervöser Symptomatologie subakute Form).

den entsprechenden Originalarbeiten entnommen).

Alter beim Exitus	Pathologische Anatomie
12 Monate	Autopsie: Milz gr. 237; Leber gr. 390; kleine Nebennieren. Histologische Untersuchung: Gaucherzellen in Milz, Lymphknoten, Knochenmark, Leber, Thymus und Solitärfollikeln des Darmes. *Im Gehirn zahlenmässige Verminderung und Atrophie der Pyramidenzellen.*
12 Monate	Autopsie: Bronchopneumonie; Milz gr. 70; Leber gr. 240; Vergrösserung aller oberflächlichen und tiefen Lymphknoten; Hufeisenniere; Foramen Botalli durchgängig. Histologische Untersuchung: Gaucherzellen in Milz, Lymphknoten, Knochenmark und Leber; Haemosiderosis.
8 Monate	Autopsie (die entsprechenden Daten sind leider nicht mitgeteilt): die Organe wurden schlecht konserviert und eigneten sich deshalb nicht zu histologischen Untersuchungen.
7 Monate	Autopsie (es fehlen makroskopische Angaben). Histologische Untersuchung: Gaucherzellen in Milz, Lymphknoten, Knochenmark, Leber und Thymus. Die das Nervensystem betreffenden Daten sind der Inaugural-Diss. von Jenny (Basel 1930), wiedergegeben von De Lange, entnommen: *In der Hirnrinde Ödem und schwere, teilweise bis zu vollkommener Zerstörung gehende Degeneration der Ganglienzellen.*
12 Monate	
11 Monate	Autopsie: Bronchitis mit bronchopneumonischen Herden; Milz gr. 185; Leber gr. 450; generalisierte Lymphadenomegalie. Histologische Untersuchung: Gaucherzellen in Milz, Lymphknoten, Knochenmark und Leber. *Die Zellen der Hirnrinde im Zustande der chronischen Zellerkrankung von Nissl (einfache Schrumpfung von Spielmeyer); viele derselben mit Vakuolen im Körper und in den Fortsätzen; Proliferation der Glia-Trabantzellen.*

Forts.

Nr	Autor	Geschlecht und Alter zu Beginn der Krankheit	Die wichtigsten klinischen Daten und die nervöse Symptomatologie
7	Oberling Woringer 1927 (III)	♀, 6 Wochen	Drittes der vier befallenen Geschwister. Spleno-Hepatomegalie; Vergrösserung der oberflächlichen Lymphknoten; progressiver Verfall. *Bewegungsarmut; Apathie; Hypertonus; Kontraktur der Gliedmassen in Beugestellung; Trisma; Strabismus convergens; Tiefenreflexe gesteigert; klonische Krämpfe; Dysphagie; respiratorischer Stridor; Erstickungsanfälle mit apnoischen Krisen und Cyanose.* Tod in extrem kachektischem Zustande.
8	Oberling Woringer 1927 (IV)	♂, 22 Tage	Viertes der vier befallenen Geschwister. Splenomegalie. *Somnolenz; ausgesprochene Apathie.* Tod durch Bronchopneumonie.
9	Dienst Hamperl 1929	♀, 2 Monate	Schwester des Falles von Stransky. Spleno-Hepatomegalie; gelbbräunliche Haut; Vergrösserung der oberflächlichen Lymphknoten. *Hypertonus; Opisthotonus; Strabismus; Temperatursteigerungen; Laryngospasmus.* Tod durch Bronchopneumonie.
10	Hoffmann Makler 1929	♂, 2 Monate	Neger; Spleno-Hepatomegalie; Vergrösserung der oberflächlichen Lymphknoten; leichte Anaemie; Leukocytose. *Hypertonus; Nackensteife; Steigerung der Sehnenreflexe.* Tod infolge steigenden Verfalls. Diagnose durch Biopsie eines Lymphknotens: Anwesenheit von Gaucherzellen.
11	Stransky 1930	♂, 4 Monate	Bruder des Falles von Dienst und Hamperl. Spleno-Hepatomegalie; Anaemie; gelbbräunliche Gesichtshaut; Blässe. *Katatonie; Hypertonus; Opisthotonus; respiratorischer Stridor; Temperatursteigerungen.* Tod durch progressiven Verfall.
12	Moncrieff 1930	♂, 10 Wochen	Splenomegalie; Anaemie; progressiver Verfall. *Opisthotonus; Steigerung der Sehnenreflexe.* Tod in marantischem Zustande.
13	Frick Friedrich 1930	♂, nicht bekannt	Ungenügende körperliche Entwicklung; Rachitis; ausgesprochene Blässe; Anaemie; Splenomegalie; Vergrösserung der oberflächlichen Lymphknoten. *Zurückbleiben der geistigen Entwicklung; leichter Hypertonus; oft spontaner Babinski.* Progressiver Verfall; Tod durch Bronchopneumonie.

Alter beim Exitus	Pathologische Anatomie
11 Monate	
1 Monat	Autopsie: Bronchopneumonie; Milz gr. 35; Leber gr. 180; Vergrösserung der tiefen Lymphknoten. Histologische Untersuchung: Gaucherzellen in Milz, Lymphknoten, Knochenmark, Leber, Lunge. *Im Gehirn die gleichen Zellveränderungen, jedoch etwas weniger ausgesprochen, wie im Fall II.*
5 Monate	Autopsie: Milz gr. 70; Leber gr. 225; Vergröss. der oberflächlichen und tiefen Lymphknoten. Hist. Untersuchung: Gaucherzellen in Milz, Knochenmark, Leber, Tonsillen, Peyer'schen Haufen, Lungen und Nebennieren. *In den Pyramidenzellen der Hirnrinde Homogenisierung des Cytoplasmas derselben.* Chemische Untersuchung: bestätigt die Diagnose (Speicherung von Cerasin).
17 Monate	Biopsische Bestätigung der Diagnose: Gaucherzellen in der Milz.
4 Monate	Autopsie: Splenomegalie; *Mikrogyrie der Occipitallappen.* Histologische Untersuchung: Gaucherzellen in Milz und Leber (die nicht vergrössert war). *Gehirn: wegen postmortaler Veränderung desselben wurde keine histologische Untersuchung gemacht.*
18 Monate	Autopsie: Milz 150 gr.; Vergrösserung der oberflächlichen und tiefen Lymphknoten. Histologische Untersuchung: Gaucherzellen in Milz, Lymphknoten, Thymus und Leber.

Forts.

Nr	Autor	Geschlecht und Alter zu Beginn der Krankheit	Die wichtigsten klinischen Daten und die nervöse Symptomatologie
14	Findlay 1931	♂, 11 1/2 Monate	Spleno-Hepatomegalie (nicht Anaemie, sondern im Gegenteil Polyglobulie). *Verlust der Fähigkeit, aufrecht zu stehen und zu gehen; Hypertonus mit Opisthotonus und Nackensteife; profuse Schweisse; Erbrechen.* Tod durch Bronchopneumonie. Diagnose durch Biopsie (Milzpunktat): Gaucherzellen.
15	Meyer 1932	♀, 6 Monate	Spleno-Hepatomegalie; Anaemie mit progressivem Verfall. *Opisthotonus; Strabismus convergens; Hemiplegie; Bradykinese; Katatonie; Dysphagie; Laryngospasmus.* Diagnose durch das Milzpunktat bestätigt: Anwesenheit von Gaucherzellen. Tod in kachektischem Zustande.
16	Dessylla Robles 1934	♂, 6 Monate	Spleno-Hepatomegalie; Vergrösserung der Halslymphknoten; schwere hypocrome Anaemie; progressiver Verfall. *Hypertonus mit Opisthotonus; Steigerung der Sehnenreflexe; Trisma; Laryngospasmus mit spastischem Husten; Erstickungsanfälle; Dysphagie.* Tod durch schwere Kachexie.
17	Meyer Woringer 1934	♀, 3 Monate	Schwester der vier befallenen Geschwister von Oberling und Woringer: Spleno-Hepatomegalie; Verdauungsstörungen; steigender Verfall. *Stillstand der geistigen Entwicklung; wachsartiger Hypertonus. Opisthotonus mit Nackensteife; Kontraktur der Gliedmassen in Beugestellung; Strabismus convergens; Trisma; Steigerung der Sehnenreflexe; Bewegungsarmut und Verzögerung der Bewegungen; Katatonie; Laryngospasmus mit spastischem Husten.* Tod in kachektischem Zustande.
18	Acuna De Filippi 1934	♂, 12 Monate	Leichte Rachitis; schwere hypocrome Anaemie; Erythroblasten und Myelocyten); Spleno-Hepatomegalie. *Generalisierte Muskelhypertonie.* Mit 19 Monaten Splenektomie (Milz gr. 600): Gaucherzellen bei der histologischen Untersuchung. Tod wenige Tage nach der Operation.
19	Nagao 1935	♂, 10 Monate	Bruder gestorben an einer Krankheit mit Spleno-Hepatomegalie, Anaemie und haemorrhagischer Diathese (wahrscheinlich Gaucher). Spleno-Hepatomegalie; hypocrome Anaemie; *Erstickungsanfälle und Laryngospasmus mit spastischem Husten.* Tod während eines dieser Anfälle.
20	Macera Brachetto Brian 1935	♀, 13 Monate	Spleno-Hep tomegalie; Blässe; hypocrome Anaemie mit Piastrinopenie; intensive Monocytose und Anwesenheit vereinzelter Myeloblasten, Myelocyten und Erythroblasten. *Strabismus convergens; respiratorischer Stridor.* Splenektomie: (Milz gr. 630). Tod 8 Tage nach der Operation.

Alter beim Exitus	Pathologische Anatomie
13 Monate	Autopsie: Milz vergrössert (Gewicht nicht wiedergegeben) mit Herden haemorrhagischer Infarzierung; Hepatomegalie und Vergrösserung der Eingeweidelymphknoten. Histologische Untersuchung: Gaucherzellen in Milz und Lymphknoten.
9 Monate	Biopsische Bestätigung der Diagnose: Gaucherzellen in der Milz.
7 Monate	Autopsie: Spleno-Hepatomegalie; (Gewichte nicht angegeben); Vergrösserung der oberflächlichen und tiefen Lymphknoten. Histologische Untersuchung: Gaucherzellen in Milz, Lymphknoten, Knochenmark, Leber und Lunge.
7 Monate	
19 Monate	Autopsie: Kongestion der Lunge; Leber vergrössert (mit weisslichen Herden von Gaucherzelleninfiltration). Histologische Untersuchung: Gaucherzellen in Milz, Leber und Lymphknoten.
11 Monate	Autopsie: Lungenödem; Milz gr. 250; Leber gr. 450; Hydronephrose links. Histologische Untersuchung: Gaucherzellen in Milz, Lymphknoten, Knochenmark, Thymus, und Leber. Chemische Untersuchung: (in Milz und Leber): Bestätigung der Diagnose einer Lipoidosis cerebrosidica (Speicherung von Cerasin).
16 Monate	Histologische Untersuchung der Milz: Gaucherzellen in grosser Zahl.

Forts.

Nr	Autor	Geschlecht und Alter zu Beginn der Krankheit	Die wichtigsten klinischen Daten und die nervöse Symptomatologie
21	Aballi Kato 1938	♀, 1 Woche	Spleno-Hepatomegalie; Vergrösserung der oberflächlichen Lymphknoten; leichte, hypocrome Anaemie; Blässe. *Opisthotonus; Nackensteife; Kontraktur der Gliedmassen in Beugestellung; Strabismus; Steigerung der Reflexe; Dysphagie; Laryngospasmus; Anfälle von Cyanose; Temperatursteigerungen.* Diagnose durch Sternalpunktat: Gaucher-Krankheit. Fortschreitender Verfall. Plötzlicher Tod durch Apnoe.
22	Koehne 1939	♂, 3 Monate	Hepato-Splenomegalie; Anaemie. *Generalisierte Hypertonie; Nackensteife; Steigerung der Sehnenreflexe; manchmal Krämpfe in Armen und Beinen; Strabismus convergens; Laryngospasmus mit apnoischen Krisen und Cyanose; Dysphagie.* Tod durch Bronchopneumonie.
23	De Lange 1939 (I)	♀, 4 Monate	Schwester des folgenden; anamnestisch diagnostizierter Fall: Spleno-Hepatomegalie. *Hypertonus mit Opisthotonus und Nackensteife; Kernig; Krampfanfälle mit Cyanose; anfallsweiser Husten; Temperatursteigerungen.* Tod im eigenen Hause (keine Autopsie).
24	De Lange 1939 (II)	♂, 2 1/2 Monate	Bruder der vorhergehenden: Spleno-Hepatomegalie; leichte Anaemie mit Leucopenie und Piastrinopenie (vereinzelt unreife myelocytische und erythroblastische Formen); mehrere kleine Bildungsanomalien (partieller Albinismus des Augenhintergrundes, Missbildung der Ohren, Angioma palatinum, Cranium missgebildet). *Stillstand der geistigen Entwicklung; Apathie; Armut der Mimik; generalisierte Hypertonie; Opisthotonus mit Nackensteife; Steigerung der Sehnenreflexe; Dysphagie; Temperatursteigerungen.* Zunehmender Verfall; Tracheobronchitis; Otitis; Tod in kachektischem Zustande.
25	Donat 1941–42	♀, 6 Monate	Spleno-Hepatomegalie; Vergrösserung der oberflächlichen Lymphknoten; leichte Anaemie; *Hypertonus mit ausgesprochenem Opisthotonus; hochgradige Steigerung der Sehnenreflexe; spastischer Husten; dyspnoische Anfälle; Erbrechen.* Progressive Verschlechterung; Tod mit Bronchopneumonie durch plötzlichen Kreislaufkollaps.
26	Ullrich 1942	♀, 6 Monate	Splenomegalie; leichte Anaemie. *Ausgesprochener Hypertonus mit Opisthotonus; Trisma; Steigerung der Sehnenreflexe; Kernig und Brudzinsky; spastischer Husten; dispnoische und apnoische Krisen; Dysphagie; Erbrechen; Singultus; starke Salivation; Temperatursteigerungen.* Progressiver Verfall; Tod in kachektischem Zustande durch Bronchopneumonie.

Alter beim Exitus	Pathologische Anatomie
4 1/2 Monate	Partielle Autopsie mit Herausnahme der Eingeweide durch einen Abdominalschnitt: Kongestion der Lunge mit haemorrhagischen Petechien auf den Sierosae; Hepatomegalie; Milz gr. 110. Histologische Untersuchung: Gaucherzellen in Milz, Lymphknoten, Lymphknötchen und Peyer'schen Haufen des Darmes, Knochenmark, Thymus, Leber, Lungen, Nieren und Nebennieren.
8 Monate	Autopsie: bronchopneumonische Herde; Milz gr. 115; Leber gr. 330. Histologische Untersuchung: Gaucherzellen in Milz, Lymphknoten, Leber und Thymus. *Überall im Gehirn, ganz besonders aber in der Rinde und in den Basalganglien, Veränderungen der Nervenzellen vom Typ der chronischen Zellerkrankung von Nissl, mit mässiger reaktiver Gliosis.* Chemische Untersuchung: Die Diagnose einer Gaucher-Lipoidosis wird bestätigt (Cerasin in der Milz sehr vermehrt).
6 Monate	
5 Monate	Partielle (abdominale) Autopsie: Es werden Stücke von Leber und Milz entnommen. Histologische Untersuchung: Gaucherzellen in beiden Organen. Chemische Untersuchung: Bestätigung der Gaucher-Lipoidosis (Speicherung von Cerasin).
8 Monate	Autopsie: Bronchopneumonie; Milz gr. 100; Leber gr. 375; Vergrösserung aller oberflächlichen und tiefen Lymphknoten. Histologische Untersuchung: Gaucherzellen in Milz, Leber, Lymphknoten und Lunge.
8 Monate	Autopsie: Chronische Bronchopneumonie mit fibrinöser Pleuritis; Milz gr. 100; Leber gr. 375; Histologische Untersuchung: Gaucherzellen in Milz, Leber, Lunge und Lymphknoten.

Forts.

Nr	Autor	Geschlecht und Alter zu Beginn der Krankheit	Die wichtigsten klinischen Daten und die nervöse Symptomatologie
27	Schairer 1942	♂, 3 Monate	Spleno-Hepatomegalie. *Somnolenz; Apathie; Hypertonus mit Opisthotonus und Nackensteife; Trismus; respiratorischer Stridor; spastischer Husten; Erstickungsanfälle; Dysphagie.* Tod durch Pneumonie.
28	Frisell 1943	♀, 2–3 Monate	Rachitis; leichte Anaemie; Spleno-Hepatomegalie. *Zurückbleiben der geistigen Entwicklung; Hypertonus mit Opisthotonus; Anfälle von Krampfhusten; respiratorischer Stridor.* Fortschreitender Verfall. Tod in kachektischem Zustande durch Bronchopneumonie gleich nach der Einlieferung ins Spital.
29	Giampalmo (I) 1945	♂, 16 Monate	Rachitis; Splenomegalie; Vergrösserung der oberflächlichen Lymphknoten; Anaemie; haemorrhagische Gingivitis; auf dem Röntgenfilm der Lungen «disseminierte, punktförmige Herde». *Generalisierter Hypertonus; Trisma; dyspnoische Anfälle.* Tod in kachektischem Zustande durch Bronchopneumonie.
30	Giampalmo (II)	♀, erste Wochen	Schwester des vorhergehenden; Frühgeburt (8 Monate); Splenomegalie; Vergrösserung der cervicalen und inguinalen Lymphknoten; Fortschreitende Unfähigkeit, zu Saugen; fortschreitender Verfall; *in der 5. Woche Auftreten von Hypertonus mit Opisthotonus; Strabismus convergens; spastischer Husten; Anfälle von Laryngospasmus mit Cyanose; Singultus; totale Dysphagie.* Tod in kachektischem Zustande während eines Erstickungsanfalles.

Alter beim Exitus	Pathologische Anatomie
8 Monate	Autopsie: Bronchopneumonie; Milz gr. 130; Leber gr. 550; Vergrösserung der Thorax- und mesenterialen Lymphknoten. Histologische Untersuchung: Gaucherzellen in Milz, Lymphknoten, Knochenmark, Leber, Thymus, Tonsillen, intestinalen Lymphknötchen, Lunge und, vereinzelt, in der Nebennierenrinde. *Sclerotische Veränderung der Nervenzellen, sowie auch solche vom Typ der chronischen Zellerkrankung von Nissl in der Hirnrinde (hier leichten Grades) und in den Zentralganglien, in der Brücke, Olive und Nuclei Dentati (hier sehr ausgesprochen); reaktive Gliosis; leichte Schrumpfung der Purkinjezellen; in einigen Nervenzellen der Zentralganglien Vakuolen und Granula einer Substanz, die histochemisch ebenso reagiert wie die in den Gaucherzellen enthaltene.*
6½ Monate	Autopsie: Bronchopneumonie; Milz gr. 110; Leber gr. 250; Histologische Untersuchung: Gaucherzellen in Milz, Lymphknoten, Knochenmark, Leber und — in grosser Zahl — in den bronchopneumonischen Herden.
20 Monate	Autopsie: Bronchopneumonie; Ductus Botalli durchgängig; Milz gr. 190; Leber gr. 400; Vergrösserung der oberflächlichen und tiefen Lymphknoten. Histologische Untersuchung: Gaucherzellen in Milz, Lymphknoten, Leber, Thymus und Lungen. *In den Nervenzellen der Hirnrinde und der Basalganglien regressive Veränderungen vom Typ der chronischen Zellerkrankung von Nissl, sowie Sklerose.* Chemische Untersuchung von Milz und Leber: Bestätigung der Diagnose einer Gaucher-Lipoidose.
6 Wochen	Keine Autopsie. Bemerkungen: Die Mutter weist spontan auf die grosse Ähnlichkeit in der »nervösen« Symptomatologie ihrer beiden Kinder hin. Vater und Mutter der Kinder sind Vettern dritten Grades und haben den gleichen Familiennamen. Der Vater ist Epileptiker. Verschiedene Onkeln und Tanten väterlicherseits sind Kropfträger. Der Ehe entstammten vier Kinder: das erste, ein Mädchen, ist jetzt 14 Jahre alt, ist körperlich und geistig unterentwickelt, hat ein mongoloides Gesicht, bräunlich pigmentierte Haut und Splenomegalie; das zweite, ein Junge, ist ebenfalls körperlich und geistig unterentwickelt, hat ein mongoloides Gesicht und mässige Splenomegalie; das dritte und vierte sind die Fälle Nr. 30 und 29 dieser Tabelle; die Mutter hatte ausserdem noch einen Abort, einen Anencephalus, im vierten Monat.

Zusammenfassung und Schlussfolgerung.

Eine Auswertung der gesamten Kasuistik lässt erkennen, dass die G. K. in den ersten beiden Lebensjahren ein durchaus besonderes, anatomisch-klinisches Bild darbietet, und dass sie, im Gegensatz zu dem im allgemeinen schleichenden, chronischen Verlauf beim älteren Kinde und beim Erwachsenen, sehr schnell einen tödlichen Ausgang nimmt.

Wenn der scheinbare Beginn der Krankheit in die ersten Lebenswochen oder Monate (erstes Semester) fällt, ist der Verlauf ganz besonders akut (akute oder maligne Form der G. K.), und der Tod tritt innerhalb des ersten Lebensjahres ein; wenn dagegen dieser Beginn jenseits des ersten Semesters liegt (etwa im ersten Lebensjahre), ist der Verlauf, obwohl immer tödlich, mehr subakut (subakute Form der G. K.), und der Tod tritt gewöhnlich im zweiten Lebensjahre ein.

Diese beiden Formen unterscheiden sich, ausser durch die Schnelligkeit des Verlaufes, klinisch von der chronischen Form des älteren Kindes und des Erwachsenen durch die sehr häufige Anwesenheit oberflächlicher Lymphknotenvergrösserungen, durch das fast konstante Fehlen der charakteristischen Hautpigmentation und der Pinguecola, durch den meist nur leichten Grad der Anaemie, durch die Seltenheit einer Piastrinopenie und vor allen Dingen einer haemorrhagischen Diathese und endlich durch das sehr häufige Auftreten eines besonderen nervösen Syndroms.

Die Krankheit fängt an mit Splenomegalie, der eine, meist weniger ausgeprägte Hepatomegalie folgt; dann tritt in etwa drei vierteln der Fälle mehr oder weniger frühzeitig die nervöse Symptomatologie zutage, fast konstant und schwer in den Fällen, deren scheinbarer Krankheitsbeginn in das erste Lebenssemester fiel, häufig und im allgemeinen weniger ausgesprochen oder unvollständig in jenen Fällen, bei denen derselbe jenseits des ersten Semesters lag. Die nervösen Symptome beginnen mit Apathie und Stillstand der geistigen und körperlichen Entwicklung, mit Bewegungs- und mimischer Armut, zu denen sich bald ein Zustand allgemeiner Hypertonie mit Nackensteife und Opisthotonus (zuerst angedeutet und vorübergehend, unter Umständen auch un-

terbrochen von hypotonischen Perioden, dann aber immer stärker und dauernder) hinzugesellt; gleichzeitig tritt (ein sehr charakteristisches Symptom) ein Strabismus convergens auf, auch dieser erst vorübergehend, dann dauernd, und eine Hyperreflexie. Die Fähigkeit, zu stehen und zu laufen, wenn sie eventuell schon bestanden haben sollte, geht wieder verloren. Sehr oft kommen zu den genannten noch andere Symptome neurovegetativer Natur hinzu, wie besonders anfallsweiser Laryngospasmus mit spastischem Husten und Erstickungszeichen, dyspnoische und apnoische Krisen (welche manchmal tödlich enden), Dysphagie, manchmal Erbrechen, profuse Schweisse und häufig Temperatursteigerungen sine Materia. Mit der Zeit schreitet die psychische Involution fort bis zur Idiotie, das Gesicht wird vollständig amimisch, und die Gliedmassen werden in Beugestellung in einer Art Dauerstarre fixiert. Unter zunehmender Verschlechterung des Allgemeinzustandes wird schliesslich das Endstadium erreicht, welches durch Kachexie mit katatonischer Starre und vollständiger Unempfindlichkeit gegen alle Reize gekennzeichnet ist. Zu diesem Zeitpunkt macht der Tod, gewöhnlich mit einer Bronchopneumonie, der Krankheit ein Ende.

Die Sektion bestätigt die Spleno-Hepatomegalie und zeigt sehr häufig, dass auch die tiefen und viszeralen Lymphknoten an dem Krankheitsprozess beteiligt sind, und die mikroskopische Untersuchung lässt noch folgende Charakteristika dieser schweren kindlichen Form erkennen:

1) die Ubiquität der Gaucherzellen, welche nicht, wie die Regel von Pick es wollte, auf Milz, Lymphknoten, Knochenmark und Leber beschränkt sind sondern sich fast überall finden können (ganz besonders häufig die Lokalisation in der Lunge, wo diese Infiltrate oft sogar den bronchopneumonischen Herden zugrunde liegen), wobei sie natürlich in den blutbildenden Organen, welche ausserordentlich reich an reticulo-histiocytären Elementen, dem Mutterboden für die Gaucherzellen, sind, auch am reichhaltigsten angetroffen werden;

2) das Fehlen einer Haemosiderosis;

3) die Veränderungen im Zentralnervensystem, welche nicht, wie man ursprünglich angenommen hatte, auf die Rinde be-

schränkt sind, sondern in allen Teilen des Gehirns, und ganz besonders in den Zentralganglien, angetroffen werden können.

Die Veränderungen im Nervengewebe bestehen vorwiegend in einer chronischen Erkrankung (im Sinne von Nissl), der Ganglienzellen, die bis zur Sklerose, manchmal mit vollständigem Untergang derselben, gehen kann. (In einigen Fällen sind auch in vereinzelten Nervenzellen Vacuolen und Granula einer Substanz beobachtet worden, welche histochemisch derjenigen in den Gaucherzellen ähnlich war.) Fast immer besteht eine mässige Gliareaktion mit Proliferation der Trabantzellen. Der Ausdehnung der Veränderungen über das ganze Gehirn entspricht eine Reichhaltigkeit des nervösen Symptombildes, welches nicht, wie ursprünglich angenommen wurde, ausschliesslich pyramidalen Charakter hat, sondern auch unzweifelhaft extrapyramidale Züge trägt.

Was die Pathogenese der nervösen Veränderungen anbetrifft (bezüglich des Problems der Pathogenese der G. K. im allgemeinen verweise ich auf meine voraufgehenden Arbeiten), so liegt die Vermutung nahe, dass dieselben durch eine nicht erfolgte Versorgung des Gehirns mit Cerebrosiden, welche in den Gaucherzellen an der Peripherie zurückgehalten werden (»Lipoidsperre« von Tropp), verursacht sein könne. Die Sachlage wäre also vielleicht, im Vergleich mit den Verhältnissen bei der nervösen Form der N. P. K. bei welcher die Veränderungen der Nervenzellen auf Phosphatid-Speicherung zurückzuführen sind, etwa entgegengesetzt. Nicht alle Forscher sind vorbehaltlos mit dieser pathogenetischen Deutung der Befunde einverstanden; wenn man jedoch berücksichtigt, dass beim Erwachsenen oder beim älteren Kinde, in einer Periode also, in der die Struktur des nervösen Gewebes schon endgültig ausgebildet ist, eine nervöse Symptomatologie fast nie in Erscheinung tritt, so liegt wohl die Vermutung nahe, dass dieselbe bei den kleinen Kindern (und ganz besonders bei den Säuglingen) durch eben den Mangel jener Cerebroside verursacht werde, die zum Reifungsprozess der Nervenzellen und Fasern, welcher ja zur Zeit der Geburt noch nicht abgeschlossen ist, erforderlich sind.

Summary and Conclusions.

An evaluation of all the casuistics indicates that in the first two years of life Gaucher's disease presents a special anatomical-clinical picture, and that in contrast to the usually slow chronic course in the older child and the adult, it soon leads to death.

When the apparent beginning of the disease comes in the first weeks or months (the first term) of life, it is especially acute (acute or malignant form of Gaucher's disease) and death follows within the first half year. When, on the other hand, the disease begins after the first term (sometime during the first year), its course, although always fatal, is less acute (sub-acute form of Gaucher's disease) and death usually follows in the second year of life.

Besides differing in the rapidity with which they move, these two forms differ clinically from the chronic form seen in the older child and the adult in the very frequent presence of superficial lymph node enlargements, the almost invariable absence of the characteristic skin pigmentation and pinguecula, the (for the most part) only slight degree of anemia, the rareness of piastrinopenia and above all hemorrhagic diathesis, and finally in the very frequent occurrence of a particular nervous syndrome.

The disease begins with splenomegaly. This is followed by hepatomegalia, usually not very severe. Then in approximately 3/4 of the cases appears, more or less early, the nervous symptomatology, continuous and severe in the cases in which the disease apparently began in the first term of life and usually less marked or incomplete in those cases in which the disease apparently began after the first term. The nervous symptoms begin with apathy, the arrest of mental and physical development, and poverty of motion and imitation, to which a condition of general hypertonia, with stiff neck and opisthotonos (at first only hinted at and of short duration, sometimes interrupted by hypotonic periods, but becoming ever more severe and persistent) is added. At the same time (this is a very characteristic symptom) a convergent strabismus appears, also of short duration in the beginning but becoming more persistent, and a hyperreflexia. The

capacity to stand and walk, if the child ever had it, is lost again. Very frequently still other symptoms of a neurovegetative character appear in addition to those mentioned, especially in the form of attacks; one may mention laryngospasm with spastic cough and signs of suffocation, dyspneic and apneic crises (often with fatal termination), dysphagia, often vomiting, profuse sweating, and frequent rises in temperature sine materia. In time the psychic involution reaches the point of idiocy, the face becomes completely amimic, and the limbs become fixed in a bent position in a kind of permanent rigidity. The general condition becomes worse and worse until finally the last stage is reached, characterized by cachexia with catatonic rigidity and complete insensitivity to all stimulation. At this point death brings the disease to an end, usually through bronchopneumonia.

Postmortem confirms the spleno-hepatomegalia and very frequently shows the deep and visceral lymph nodes also affected by the disease. Microscopic examination reveals the following characteristics of this severe infant form.

1) The ubiquity of the Gaucher cells, which are not confined, in accordance with Pick's rule, to the spleen, lymph nodes, bone marrow, and liver, but may be found almost everywhere (very frequently localized in the lung; hence these infiltrations often pave the way for the aforementioned bronchopneumonia), wherefore they are naturally also found in quantity in the blood-forming organs, which are extraordinarily rich in the reticulohistiocytary elements, the native ground of the Gaucher cells.

2) The absence of a hemosiderosis.

3) The changes in the central nervous system, which are not, as was originally assumed, confined to the outer part of the brain but may be found all through it, and particularly in the central ganglia.

The changes in the nerve tissue consist predominantly in a chronic disease (in the sense of Nissl) of the ganglion cells. It may go as far as sclerosis, often with complete decline. (In a few cases individual nerve cells were observed to have vacuoles and granules of a substance which was histochemically similar to that in the Gaucher cells.) But there is always a moderate glia

reaction with proliferation of the satellite cells. The richness and variety of the nervous symptom picture corresponds to the extension of the changes throughout the entire brain; this picture has not, as was originally assumed, a pyramidal character only, but undoubtedly also has extrapyramidal features.

With regard to the pathogenesis of the nervous changes (concerning the problem of the pathogenesis of Gaucher's disease in general I refer the reader to my earlier works), one suspects that they may be attributable to deficiencies in the supply of cerebrosides to the brain. These cerebrosides are kept back in the Gaucher cells on the periphery (the »lipoid stockade» of Tropp). The situation would thus seem to be about the reverse of the situation in the nervous form of Niemann-Pickschen disease, where the changes in the nerve cells are due to over-supply of phosphatides. Not all research men are willing to subscribe without qualification to this pathogenetic interpretation of the condition; but if one considers that a nervous symptomatology almost never appears in the adult or the older child — who has reached a point at which the structure of the nervous tissue is already definitive in form — then it is not far-fetched to assume that this symptomatology in small children (and particularly in infants) is caused by just the lack of that cerebroside which is required in the maturing process of the nerve cells and fibers, a process not yet concluded at the time of birth.

Résumé et conclusion.

Un aperçu général de toute la casuistique de la maladie de Gaucher montre que cette maladie dans les deux premières années de la vie offre un caractère anatomique clinique tout à fait spécial, contraire au cours, généralement insidieux et chronique, qu'elle présente chez l'enfant plus âgé et chez l'adulte; elle finit très rapidement par la mort.

Quand les premiers symptômes de la maladie se montrent pendant les premières semaines ou les premiers mois de la vie (premier semestre), son cours est tout spécialement aigu (forme aiguë ou maligne de la maladie de Gaucher); la mort arrive pendant la première année de la vie. Mais quand ces symptômes

se présentent après le premier semestre (au cours de la première année) son cours, quoique toujours mortel, est plutôt subaigu (forme subaiguë de la maladie de Gaucher) et la mort arrive généralement pendant la deuxième année de la vie.

Ces deux formes se distinguent cliniquement de la forme chronique chez l'enfant plus âgé et chez l'adulte non seulement par la rapidité de leur cours, mais aussi par la présence très fréquente de l'hypertrophie des ganglions lymphatiques superficiels et par le manque presque constant de pigmentation cutanée et de pinguecula et encore par un léger degré d'anémie ainsi que par la rareté de »piastrinopenie» et avant tout d'une diathèse hémoragique et finalement par la présence fréquente d'un syndrome nerveux spécial.

La maladie commence par une splénomégalie suivie d'une hépatomégalie généralement moins prononcée; puis, dans environ les 3/4 des cas, il se produit la symptomatologie nerveuse presque constante et grave dans les cas où les symptômes visibles de la maladie se déclarent durant le premier semestre de la vie; mais souvent et généralement moins prononcée, si ces symptômes se déclarent après l'âge de 6 mois. Les premiers symptômes nerveux sont l'apathie et un arrêt du développement psychique et corporel, difficulté de mouvement et de mimique suivie bientôt d'hypertonie générale avec rigidité de la nuque et »opisthotonus» (d'abord symptomatique et temporaire, souvent aussi interrompu par des périodes hypotoniques, puis plus accentuée et plus durable) et en même temps un strabisme convergent (symptôme très caractéristique), celui-ci d'abord temporaire, puis durable, et de même une hyperreflexie. La capacité de se tenir debout et de courir disparaît, si toutefois l'enfant l'avait déjà possédée. Très souvent ces symptômes indiqués sont accompagnés d'autres symptômes de nature neurovégétative, comme par exemple des crises de laryngospasmes avec toux spasmodique et symptômes d'étouffement et crises »apnoiques» (qui causent souvent la mort), dysphagie, parfois vomissements, transpiration, abondante et souvent élévation de température sine materia. Peu à peu l'évolution psychique regresse et aboutit à l'idiotie, la face perd toute expression et les membres s'immo-

bilisent dans une position courbée jusqu'à une sorte de rigidité permanente. Durant une aggravation croissante de l'état général se produit la phase finale caractérisée par la cachexie avec raideur catatonique et insensibilité complète à toute excitation. A ce moment la mort est généralement provoquée par une bronchopneumonie.

La dissection confirme la splenohépatomegalie et montre très souvent que l'hypertrophie des ganglions profonds et viscéraux participe au procès de la maladie. L'examen microscopique montre en outre les caractéristiques suivantes de cette forme infantile grave:

1. L'ubiquité des cellules de Gaucher, qui se trouvent non seulement dans la rate, dans les noeuds lymphatiques, dans la moelle des os et dans le foie, comme la règle de Pick le voulait, mais qui peuvent être presque partout (très souvent elles sont localisées dans le poumon, où leur infiltration forme, souvent même, la base de foyers bronchopneumoniques). Elles sont naturellement plus abondantes dans les organes producteurs de sang qui sont extrêmement riches en éléments réticulo-histiocytaires, base maternelle des cellules de Gaucher;

2. le manque d'une hémosidérose;

3. les changements dans le système nerveux central qui, contrairement à ce qu'on supposait originairement, ne sont pas bornés à le pallium, mais peuvent se trouver dans toutes les parties du cerveau, tout spécialement dans les ganglions centraux.

Les troubles dans le tissu nerveux consistent principalement en une maladie chronique (d'après Nissl) des cellules ganglionnaires, qui peut causer la sclérose entrainant parfois la destruction complète de ces cellules. (Dans quelques cas on a observé dans des cellules nerveuses isolées des vacuoles et des granules d'une substance histochimiquement semblable à celle des cellules de Gaucher.) Il y a presque toujours une réaction gliale modérée. Une ampleur du tableau des symptômes nerveux qui n'a pas un caractère exclusivement pyramidal, comme on le supposait d'abord, mais qui sans doute a aussi des traits extra-pyramidaux, correspond au dégré des troubles dans le cerveau entier.

En ce qui concerne la pathogénie des troubles nerveux (pour

le problème de la pathogénie de la maladie de Gaucher en général, je me réfère à mes ouvrages précédents) il est à supposer qu'ils ont été causés par le manque au cerveau de cérébrosides retenus dans les cellules de Gaucher à la périphérie (»lipoid-sperre» de Tropp). La situation serait donc probablement contraire aux conditions de la forme nerveuse prévalant au cas de la maladie N. P., où les changements des cellules nerveuses scnt dûs à l'accumulation de phosphatides. Les investigateurs ne sont pas tous d'accord sans réserve sur cette interprétation pathogénitique de l'état, mais quand on considère que chez l'adulte ou chez l'enfant plus âgé, donc dans une période, où la construction du tissu nerveux est déjà définitivement terminée, une symptomatologie n'apparait presque jamais, on est incliné à supposer que chez les enfants jeunes (spécialement chez les nourrissons) elle est causée par le manque de ces cérébrosides nécessaires au procès de maturation des cellules nerveuses et des fibres, qui n'est pas encore terminée au moment de la naissance.

Resumen y conclusión.

Una avaluación general de las casuísticas comunes de la enfermedad de Gaucher muestra que esta enfermedad en los dos primeros años de vida ofrece un carácter anatómico-clínico enteramente especial y contrario a la marcha, generalmente insidiosa y crónica, que presenta en niños de mayor edad y en adultos. Termina muy rápidamente con la muerte.

Al aparecer los primeros síntomas de la enfermedad durante las primeras semanas o los primeros meses de vida (primer semestre), su marcha es especialmente aguda (forma aguda o maligna de la enfermedad de Gaucher); la muerte viene durante el primer año de vida. Pero cuando estos síntomas se presentan después del primer semestre (durante el primer año), su marcha, aunque mortal, es más bien sub-aguda (forma sub-aguda de la enfermedad de Gaucher) y la muerte viene generalmente durante el segundo año de vida.

Estas dos formas se distinguen clínicamente de la forma crónica en el niño de mayor edad y en el adulto no sólo por la rapidez de su curso sino también por la presencia, muy frecuente,

de la hipertrofia de los ganglios superficiales linfáticos y por la falta casi constante de pigmentación cutánea y de pinguécula, y también por un grado generalmente ligero de anemia, por la escasez de »piastrinopenie», por una diátesis hemorrágica y por la presencia frecuente de un síndrome nervioso especial.

La enfermedad comienza por una esplenomegalia seguida de una hepatomegalia generalmente menos pronunciada; después, aproximadamente en tres cuartas partes de los casos, se produce la sintomatología nerviosa casi constante y grave en los casos en que los síntomas visibles de la enfermedad se dan a conocer durante el primer semestre de vida; más a menudo y generalmente menos pronunciados si estos síntomas aparecen después de los 6 meses de vida. Los primeros síntomas nerviosos son la apatía y una detención del desarrollo físico y corporal, dificultad de movimiento y de la mímica, seguida muy pronto por una hipertonía general con rigidez en la nuca y opistótonos (primero sintomático y después más acentuado y duradero) y al mismo tiempo un estrabismo convergente (síntoma muy característico), primero temporario y después más duradero, y una hiperreflexia. La capacidad de estar de pie y de correr desaparece, en caso de que el niño la hubiera ya tenido antes. Muchas veces estos síntomas que acabamos de mencionar son acompañados por otros síntomas de naturaleza neurovegetativa, como por ejemplo la crisis de laringoespasmos con tos espasmódica y síntomas de sofocación y las crisis »apnóicas» (que muchas veces son mortales), disfagia, a veces vómitos, transpiraciones abundantes y a veces elevación de la temperatura *sine materia*. Poco a poco la evolución psíquica reaparece y termina en idiotismo, la cara pierde su expresión y los miembros se inmovilizan en una posición encorvada hasta llegar a una especie de rigidez permanente. Durante una creciente agravación del estado general se produce la fase final, caracterizada por caquexia con tiesura catatónica e insensibilidad completa a toda exitación. En este momento la muerte es provocada generalmente por una bronconeumonía.

La disección confirma la esplenohepatomegalia y muestra muy a menudo que la hipertrofia de los ganglios profundos y viscerales participa en el proceso de la enfermedad. El examen

microscópico muestra además las siguientes características de esa forma infantil grave:

1. La ubicuidad de las células de Gaucher, que se encuentran no sólo en el bazo, en los nudos linfáticos, en la medula de los huesos y en el hígado, como la tesis de Pick expresó, sino que se encuentran en todas partes (muy a menudo son localizadas en el pulmón, donde su infiltración forma incluso la base de focos bronconeumáticos). Son naturalmente más abundantes en los órganos productores de sangre, los cuales son muy ricos en elementos retículohistiocitereos, base maternal de las células Gaucher.

2. Falta de hemosidérosis.

3. Las alteraciones del sistema central nervioso (cerebro), las cuales, contrariamente a lo que se suponía antes, no se limitan a le pallium, sino que pueden encontrarse en todas las partes del cerebro, especialmente en los ganglios centrales.

Las perturbaciones en los tejidos nerviosos son principalmente una enfermedad crónica (según Nissl) de las células ganglionarias que pueden ocasionar esclerosis y dar origen a veces a la destrucción completa de estas células. (En algunos casos, en las células nerviosas aisladas, se han observado vacuolas y gránulos de una sustancia histoquímicamente semejante a la de las células de Gaucher). Casi siempre hay una reacción glial, moderada, con proliferación de las células satélites. Una amplificación del cuadro de síntomas nerviosos, que no tiene un carácter exclusivamente piramidal, al contrario de lo que se suponía al principio, pero que sin duda tiene tambien rasgos extrapiramidales, corresponde al grado de desórdenes en todo el cerebro.

En cuanto a la patogenia de las perturbaciones nerviosas (en lo que se refiere a la patogenia de la enfermedad de Gaucher en general, me remito a mis obras precedentes), se puede suponer que han sido causadas por la falta en el cerebro de cerebrósidos retenidos en la periferia de las células de Gaucher (Barrera de lipoides de Tropp). La situación sería entonces probablemente contraria a las condiciones de la forma nerviosa predominante en el caso de la N. P. K. (enfermedad de N. P.), en la cual las alteraciones de las células nerviosas son debidas a la acumula-

ción de fosfatidos. No todos los investigatores estan de acuerdo sobre esta interpretación patogénica de las alteraciones. Al tomar, sin embargo, en consideración que en adultos o en niños de mayor edad, es decir, en un período cuando la construcción de los tejidos nerviosos está definitivamente terminada, no aparece casi nunca una sintomatología, es fácil pues suponer que en niños jóvenes (especialmente en los años de pecho), aquélla es consecuencia de la ausencia de estos cerebrósidos necesarios en el proceso de maduración de las células nerviosas y de las fibras, que no están todavía terminadas en el momento de nacimiento.

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Anmerkung bei der Korrektur.

Eine erschöpfende klinische Arbeit über die chronische Form der kindlichen G. K. von Bulgarelli, aus der Schule von De Toni — Genova, ist im Druck: Studio della forma cronica del morbo di Gaucher; considerazioni sulla patogenesi della tesaurismosi cerebrosidica e di alcuni suoi sintomi. Policlin. Infant., Marzo, 1948.

AUS DEM KRANKENHAUS VARDÖ, NORWEGEN UND DEM STADTKRANKENHAUS HADERSLEV, DÄNEMARK.

Ulcus ventriculi et duodeni bei Kindern.

Von

SVEN DAHL.

Nach TH. R. BROWN können beide Geschlechter in allen Altersklassen Magengeschwüre bekommen. Trotzdem rechnen die Wenigsten damit, dass Kinder unter 15. Jahren dieses Leiden haben können. S. MONRAD behauptet, dass es das Ulcus ventriculi, so wie es bei Erwachsenen zu finden ist, im Kindesalter nicht gäbe, mit Ausnahme ganz seltener Fälle bei Mädchen im Pubertätsalter, wogegen das Ulcus duodeni bei Kindern keineswegs selten zu finden sei.

In der Litteratur über die Magengeschwüre und deren Behandlung findet man in Bezug auf die Erwachsenen sehr viel angeführt, während die Verhältnisse bei den Kindern nur selten erwähnt werden.

Von Magengeschwüren, die bei Säuglingen nach Verbrennungen oder septischen Infektionen entstehen, wird in dieser Arbeit ganz abgesehen.

Aus der Litteratur scheint hervorzugehen, dass bei Kindern das Hauptsymptom der Magengeschwüre Hämatemesis ist, während die typischen dyspeptischen Beschwerden, so wie sie bei den Erwachsenen vorkommen, mehr in den Hintergrund treten. Auch wird behauptet, dass die Prognose immer dubia sei, da Perforationen und profuse Blutungen vorkommen können. Aus den wenigen Fällen meiner Beobachtung habe ich nicht den Eindruck bekommen, dass das Magengeschwür bei Kindern viel anders verläuft, als bei Erwachsenen, was aus dem Folgenden hervorgeht.

Ulcus ventriculi bei Kindern.

Während meiner Tätigkeit im Vardöer Krankenhaus in der kriegsverwüsteten Finnmark in den Jahren 1945—46 behandelte ich im Ganzen 16 Patienten mit Gastritis pylorica, 12 mit Ulcus duodeni, 29 mit Ulcus ventriculi, einen Patienten, der ein Ulcus ventriculi et duodeni hatte und 4 mit Ulcus juxtapyloricum. Von diesen 62 Patienten waren 3 unter 15 Jahren, Knaben, die alle drei ein einfaches Ulcus ventriculi hatten.

♂, 9 Jahre, im November 1945 eingebracht mit akuten abdominalen Symptomen. Hatte spät-nachmittags heftige Schmerzen im obersten Teil des Abdomens bekommen mit Übelkeit und Erbrechen. Er gab an, dass er im Laufe der letzten 9 Monate kurz vor den Mahlzeiten Schmerzen im Epigastrium gehabt hatte, sowie Ructus und Pyrosis. Obstipationsperioden hatte er nie gehabt. Die Kost war im letzten Jahre knapp gewesen — meist Fisch getrocknet, gesalzen, geräuchert — wenig Kartoffeln und Rüben, Trockenmilch. War 2 Jahre auf der Flucht vor den Deutschen in Sibirien gewesen. Im letzten Jahre war er keiner psychischen Belastung ausgesetzt gewesen.

Das Röntgenbild zeigte eine erbsengrosse Nische an der kleinen Curvatur. Diese verschwand nach einer Kur mit Milch und Eiern, steigend zu pürierter Kost mit reichlichem Zusatz von Vitamin C und B.

♂, 10 Jahre, eingebracht im Januar 1946 zur Beobachtung wegen Magenbeschwerden. Hatte 2 Jahre hindurch Perioden mit zunehmenden Schmerzen im Epigastrium, besonders in der dunkeln Zeit (Polarland mit 2 Monaten Dunkelheit). Die Schmerzen kamen besonders, wenn er gesalzene oder geräucherte Fische gegessen hatte. Gleichzeitig Ructus, Pyrosis und Übelkeit, seltener Erbrechen. Als die Schmerzen zunahmen, wurde der Appetit schlechter und er verlor an Gewicht. Hatte die Kriegsgreuel mit Bombardements und Abbrennen der Städte erlebt.

Das Röntgenbild zeigte eine gut erbsengrosse Nische beim Angulus ventriculi. Diese verschwand vollständig nach 6 Wochen Diät mit Milch, Eiern, Püreekost und reichlichem Zusatz von Vitamin C.

♂, 14 Jahre eingebracht im Mai 1946. Hatte während eines Fischfanges von einigen Tagen heftige Schmerzen im oberen Teil des Abdomens bekommen. Einige Wochen früher auf einem Fischfang ähnliche Schmerzen geringeren Grades. (Fischerei auf dem Eismeer ist äusserst anstrengend mit wenig Gelegenheit für Schlaf und regelmässige Mahlzeiten). Er hatte häufig Ructus, saures Aufstossen, keine Übelkeit oder Erbrechen. Hatte den Krieg und seine Greuel erlebt.

Das Röntgenbild zeigte eine kaum bohnengrosse Nische auf der Rückseite des Magens nahe der kleinen Curvatur beim Angulus ventriculi. Nach 6 Wochen Diät restierte eine sternförmige Figur an der Stelle des Ulcus.

Diese 3 Knaben hatten dyspeptische Symptome mit recht ausgesprochenen Schmerzen. Keiner von ihnen hatte Hämatemesis gehabt. Die Diätbehandlung hatte gute Wirkung.

Das folgende Beispiel stammt aus Haderslev im südlichen Teile Dänemarks. Der Fall ist von etwas anderem Charakter, ich habe ihn jedoch mitgenommen, weil sein erster Krankenhausaufenthalt in den Kinderjahren stattfand.

♂, 34 Jahre, im November 1947 eingebracht mit Hämatemesis und Meläna, welche plötzlich wärend einer Defäkation auftraten ohne dass sich vorher Symptome gezeigt hatten. Trotz Bluttransfusion starb der Patient kurz nach der Einbringung. Ein altes Journal zeigte (vom Jahre 1923), dass der Patient im Alter von 11 Jahren eine ähnliche plötzliche profuse Hämatemese gehabt hatte. Wurde damals mit Eiswasser und Eisbeutel behandelt. Nach Verlauf von 6 Wochen als gesund entlassen, in den folgenden 23 Jahren symptomfrei. Die Sektion ergab ein bohnengrosses Ulcus an der kleinen Curvatur, etwa 8,5 cm über dem Pylorus mit einem erodierten Gefäss. Einige cm über diesem fand sich eine narbenartige Veränderung, die vermutlich der Rest des Geschwürs war, das der Patien im Alter von 11 Jahren gehabt hatte.

Diese 4 Fälle von Ulcus ventriculi bei Knaben sprechen entschieden dagegen, dass dieses Leiden nur bei Mädchen im Pubertätsalter zu finden ist.

Ulcus duodeni bei Kindern.

Die hier angeführten Fälle stammen alle aus Haderslev in Dänemark. Unter einem Material von 414 Patienten mit Ulcus duodeni und 7 Patienten mit Ulcus ventriculi waren 9 Kinder mit Ulcus duodeni, wo die Diagnose mehr oder weniger sicher röntgenologisch festgestellt wurde. Die einzelnen Fälle sollen hier kurz besprochen werden.

1) ♀, 7 Jahre, eingebracht im August 1946, einziges Kind. Die Mutter ein Jahr vorher an Leukämie gestorben. Mit Ausnahme leichter Kinder-

krankheiten früher gesund. Seit einem Jahr Perioden mit Unpässlichkeit, schlechtem Appetit, Kurzatmigkeit und häufigem Erbrechen, oft im Anschluss an die Mahlzeiten. Diese Anfälle dauerten 2—7 Tage dann allmähliche Besserung. Patient wurde während eines Anfalles, der seit 24 Stunden andauerte, eingebracht. Klagt über Magenschmerzen, fast stündliches Erbrechen. Kein Fieber, etwas Durst, schlechter Appetit. Gibt Schmerzen in der Nabelgegend an. Objektiv ein normales Kind ohne Druckempfindlichkeit im Abdomen.

BTdr. 115/90, SR 1 mm, Hb 94 %, Urin: albumen +, Zucker +, Aceton + +, Diacet +. Nüchtern Blutzucker 55 mg, Mantoux 1/1000 mg +, Ewalds Probemahlzeit: 26 ml, Acidität 4/50, Fäces + blut., Erbrochenes + Günzburg.

Röntgen des Magens zeigt eine Intermediärschichte von 7 cm. Der Bulbus ist dauernd deformiert mit einer Retraktion der grossen Curvatur. Auf einigen Bildern ein nischenähnlicher Schatten. Nach 4 Stunden Retention +.

Nach 6 Wochen Pureediät ist das Kind gesund.

Diagnose: Ulcus duodeni.

2) ♂, 9 Jahre, eingebracht im Oktober 1944. Hatte seit etwa 2 Jahren über Schmerzen quer über dem Epigastrium geklagt, besonders während und nach den Mahlzeiten. Hat danach nicht recht essen wollen. Kein Ructus, Pyrosis oder Erbrechen. Die Schmerzen verschwinden gewöhnlich spontan nach 2—3 Wochen. Hat abgenommen. Stuhl normal und Meläna. Hat Neigung zu Erkältungen und Bronchitis. Objektiv Microadenitis universalis. Patient ist mager, sonst normale Verhältnisse, keine Abdominalempfindlichkeit. Nach 10 tägiger Bettruhe traten leichte Magenschmerzen und Erbrechen auf, darauf Wohlbefinden.

SR 4 mm, Hb 101 %, Fäces + Blut, Mantoux +, Ewalds Probemahlzeit: 26 ml, Acid. 5/65, + Grünzburg. Fastensecret 16 ml, Acid. 23/25, + Günzburg.

Röntgen des Magens zeigte den Bulbus mit grobem, unregelmässigen Schleimhautrelief und Defiguration. Keine sichern Nischen. 4 Wochen Pureediät hatten gute Wirkung. Der Bulbus bekam im Röntgenbild normales Aussehen.

Diagnose: Gastritis pylorica-obs. pro Ulcus duodeni.

3) ♂, 10 Jahre, eingebracht im Februar. Hat seit 3—4 Jahren über Magenschmerzen geklagt, teils im Zusammenhang mit den Mahlzeiten, teils ohne Veranlassung. Im letzten Jahre haben die Schmerzen an Stärke zugenommen und es kommt oft zu Erbrechen der Speisen. Er hat an Gewicht abgenommen. Im letzten Halbjahr ab und zu melänafarbige Stühle. Hat Oxyuren. Objektiv normale Verhältnisse bis auf etwas Empfindlichkeit im Epigastrium und um den Nabel.

Ewalds Probemahlzeit: 102 ml, Acid. 5/60, (+) Günzburg. Die übrigen Laboratoriumsuntersuchungen waren normal.

Röntgen: Bulbus schlecht gefüllt mit grobem Schleimhautrelief. Die Konturen deformiert.

Wurde mit 4 Wochen Ulcuskur (Püreekost) vollständig geheilt.

Diagnose: Gastritis pylorica- obs. pro Ulcus duodeni.

4) ♂, 11 Jahre, eingebracht im November. In den letzten Jahren mehrere Perioden mit täglichen Bauchschmerzen begleitet von Übelkeit und oft Erbrechen. Hat manchmal 5—6 Schmerzanfälle täglich. In den letzten Wochen weniger Erbrechen, aber »Salzwasseraufstossen». Die Schmerzanfälle kommen auch nachts. Der Stuhl ist einigemal sehr dunkel, fast schwarz gewesen.

Objektiv ein schmächtiges, fast mageres Kind. Leichte Empfindlichkeit an der linken Curvatur, sonst normaler Befund.

Ewalds Probemahlzeit: 70 ml, Acidität 8/55, + Günzburg.

Magenröntgen zeigte den Bulbus schlaff, teils atonisch mit schwacher Peristaltik und einer Intermediärschicht von 8 ml. Der Bulbus zeigt ein unregelmässiges Schleimhautrelief und recht andauernde unregelmässige Kontur.

Wurde mit 4 Wochen Püree-Ulcuskur geheilt.

Diagnose: Gastritis pylorica- obs. pro Ulcus duodeni.

5) ♀, 13 Jahre, eingebracht im Juli 1946. Die Mutter hatte Magengeschwür. 1/2 Jahr vor der Einbringung begann Drücken im Epigastrium ganz unabhängig von den Mahlzeiten, aber doch manchmal Verschlechterung nach dem Essen. Sonst keine dyspeptischen Erscheinungen. Im letzten Monat wurden die Schmerzen stärker. Objektiv nur geringe Empfindlichkeit links im Epigastrium, sonst Alles normal.

Ewalds Probemahlzeit: 105 ml, Acidität 35/68. Fastensekret 16 ml, Acid. 7/22.

Die übrigen Laboratoriumsuntersuchungen normal. Röntgen zeigte einen kleinen Bulbus duodeni, spastisch, korallenstockförmig und auf einem Bild war eine nischenähnliche Bildung zu sehen.

Mit 4 Wochen Püreekost wurde das Kind geheilt.

Diagnose: Ulcus duodeni.

6) ♀, 13 Jahre, eingebracht im Oktober 1946. Seit etwa einem Jahre Magenbeschwerden, bestehend aus Übelkeit und Drücken im Epigastrium ein paar Stunden nach den Mahlzeiten, hie und da als Hungerschmerz, aber ohne Linderung durch Speisenaufnahme. Die Schmerzen kommen oft während Fahrrad- und Fusstouren. Selten Erbrechen, etwas Pyrosis und Ructus, oft nächtliche Schmerzanfälle. Die Schmerzen ziehen manchmal von Epigastrium in den Unterleib. Menarche noch nicht eingetreten. Objektiv besteht Empfindlichkeit an der Spitze des Epigastriums, sonst normale Verhältnisse.

Ewalds Probemahlzeit: 110 ml. Acid. 60/86. Fastensekret 8 ml, Kongo 0.

Fall 9

Das Röntgenbild zeigte den Bulbus spastisch mit unregelmässigen Konturen, aber keine deutliche Nischen.

Mit Püreekost wird das Kind in 4 Wochen symptomfrei.

Diagnose: Gastritis pylorica- obs. pro Ulcus duodeni.

7) ♂, 14 Jahre, Vater hatte Ulcus corporis ventriculi. Ein Jahr vor der Einbringung Schmerzen in der Nabelgegend mit Übelkeit und Erbrechen, was sich durch Milchdiät besserte. In den letzten 4 Monaten wieder Schmerzen um den Nabel, unabhängig von den Mahlzeiten, sowie Ructus und Pyrosis, Übelkeit und Erbrechen. Hat etwas dänischen Tabak geraucht. Objektiv ein zart gebauter Junge mit Empfindlichkeit im Epigastrium und um den Nabel. Sonst normale Verhältnisse.

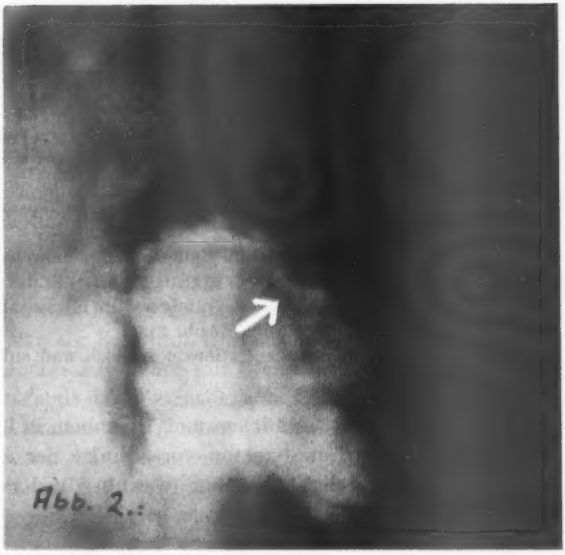
Ewalds Probemahlzeit: 125 ml, Acidität 45/95, Fastensecret 16 ml. Kongo 0.

Röntgen zeigt den Bulbus mit grobem, unregelmässigen Schleimhautrelief, dauernd Defiguration, aber keine sichern Nischen.

Durch 4 wöchige Püreediät klinisch und subjektiv geheilt.

Diagnose: Gastritis pylorica-obs. pro Ulcus duodeni.

8) ♂, 14 Jahre, eingebracht im Dezember 1945. Im letzten Monat Schmerzen links im Epigastrium, am stärksten morgens. Keine sichere



Fall 9

Schmerzlinderung nach dem Essen, sonst keine dyspeptischen Symptome. Vermeidet fette Speisen, was etwas half.

Ewalds Probemahlzeit: 140 ml, Acidität 8/75, + Günzburg. Fastensekret 20 ml. Kongo 0.

Röntgen zeigte den Bulbus spastisch und auf einem Bild im 1. Schrägdiameter ist eine erbsengrosse Nische nach unten mit fächerförmigem Schleimhautrelief zu sehen.

Wurde eine Woche auf Milchkur gesetzt, und darauf Püreekost durch 4 Wochen. Seitdem gesund.

9) ♀, eing. 1945, hat seit ihrem 9. Lebensjahr 1—2 tägige Perioden von zeitweisen Schmerzen im Abdomen. Die Schmerzen halten ein paar Stunden an und sind ziemlich diffus, begleitet von Übelkeit, aber kein Erbrechen. Manchmal Diarrhöe im Anschluss an die Schmerzen, + Meläna, + Hämatemesis. Wurde zum ersten Mal eingebracht im Juli 1945 wegen einer neuen Schmerzperiode, möglicherweise hervorgerufen durch Erkältung. Die objektive Untersuchung ergab normale Verhältnisse.

Ewalds Probemahlzeit: 48 ml. Acidität 0/23.

Das Röntgenbild des Ventricels zeigte im Bulbus eine central gelegene Nische (Abb. 1).

Keine Retention nach 4 Stunden.

Wurde mit Püreediät durch 4 Wochen erfolgreich behandelt.

Nach der Entlassung hielt das Kind Schonungsdiät durch etwa ein Jahr. Darauf allmähliche Kostzulage.

Im Alter von 13 Jahren (September 1947) kamen wieder Schmerzen im Epigastrium. Im Anfang nur, wenn sich der Patient bückte, später ab und zu Schmerzen nachts, zuletzt Schmerzen 1/2—1 Stunde nach den Mahlzeiten.

Sie sind so heftig, dass das Kind sich vor Schmerzen zusammenkrümmt.

Ausser Übelkeit keine dyspeptischen Symptome. Menarche noch nicht eingetreten.

Röntgen des Magens zeigte diesmal eine randgestellte nischenähnliche Bildung an den Profilbildern des Bulbus (Abb. 2).

Nach 4 Wochen Püreediät ist die Patientin klinisch und subjektiv gesund.

Von diesen 9 Fällen sind 4 Mädchen und 5 Knaben, in keinem Falle kamen gefährliche Hämatemesen vor. Einige der Kinder scheinen zuhause Meläna gehabt zu haben, was aber im Krankenhause nicht nachzuweisen war.

Diskussion.

Es kann gleich festgestellt werden, dass es eine profuse Blutung nur in einem Falle von Ulcus ventriculi gab (vom Jahre 1923). Meläna konnte in 2 Fällen nur anamnestisch angenommen, aber chemisch in keinem Falle nachgewiesen werden. Alle hatten mehr oder weniger heftige Schmerzen, in der Regel im Epigastrium. Nur ein Fall von Ulcus ventriculi hatte keine Schmerzen, aber dieser Fall bildet in vieler Beziehung eine Ausnahme.

7 der Patienten hatten Übelkeit und 6 hatten ziemlich regelmässig Erbrechen, während weitere 2 nur seltenes Erbrechen hatten. Ructus gab es als Symptom bei 3 mit Ulcus ventriculi und bei 2 mit Ulcus duodeni, während Pyrosis bei 6 der Kinder vorkam, wovon 3 Ulcus duodeni hatten. Herabgesetzter oder schlechter Appetit wurde in 4 Fällen berichtet, während Gewichtsabnahme nur bei einem Kinde festzustellen war.

Die 3 Knaben mit Ulcus ventriculi hatten auf dem Röntgenbild sichere Nischen, während dies nur bei 4 der 9 Kinder mit

Ulcus duodeni der Fall war. Andererseits war der Bulbus in allen restierenden 5 Fällen so stark deformiert, dass die Diagnose recht wahrscheinlich wurde.

Von sämtlichen 13 Magenpatienten waren 9 Knaben und 5 Mädchen, ein Verhältnis, das nicht viel von dem bei Erwachsenen abweicht. Alsted fand unter 629 erwachsenen Ulcuspatienten 442 männliche und 178 weibliche.

FORSELL fand 6 Fälle von Ulcus duodeni und 1 von Ulcus ventriculi bei Kindern im Laufe einiger Jahre in einem einzigen Krankenhaus in Helsingfors (Finnland). Die Synmptomatologie wich in diesen Fällen nicht viel von den oben skizzierten ab. Jedoch hatte ein Kind mit Ulcus ventriculi Hämatemesis.

Wasbergs 2 Mädchen mit Ulcus duodeni hatten Erbrechen und Schmerzen als das Wesentliche im Bilde, während das eine ausserdem Meläna hatte. ALSTED (I) erwähnt bei seinem 11-jährigen Knaben mit Ulcus duodeni explosives Erbrechen, Schmerzen im Epigastrium, Schmerzlinderung nach Speiseaufnahme, schlechten Appetit und leichte Gewichtsabnahme.

GUTRIS meint, dass Blutungen das charakteristische Symptom bei Kindern sind, wogegen Hungerschmerzen und lokale Empfindlichkeit fehlt. Manchmal ist Perforationsperitonitis das erste Symptom. Hier muss erwähnt werden, dass Gutries Kinder unter 3—4 Jahre alt sind und also von dem Material abweichen, das hier erörtert wird. Ich habe diese Arbeit nur erwähnt, weil sie zu zeigen scheint, dass absolut ein Unterschied besteht in den Ulcussymptomen bei kleinen Kindern und Kindern im schulpflichtigen Alter. Wenn man daher das Ulcusproblem bei Kindern diskutiert, muss man gleichzeitig angeben, aus welchen Altersklassen man das Material hat. DONOVAN u. SANTULLI sind anscheinend hierüber nicht ganz klar, erwähnen aber doch, dass in den Altersklassen über 6—7 Jahre das klinisch-anamnestische Bild eben so klar sein kann wie beim Erwachsenen. Diese Verfasser behaupten auch, dass die Blutungen das häufigste Symptom sind. Sie erwähnen ebenfalls, dass Magensaftanalysen nicht praktisch sind und irreführen können, ein Ergebnis, zu dem man auch bei den in dieser Arbeit erwähnten Fällen kommt.

Nun ist Ewalds Probemahlzeit bei Weitem keine ideale Unter-

suchungsmethode, man erwartet aber doch, dass mindestens eine von zwei Untersuchungen freie Salzsäure zeigen sollte, wenn das Kind Magengeschwür hat. Dies ist auch nicht immer der Fall. So hatte der Fall *9* viermal Achylie bei Ewalds Probemahlzeit, trotzdem er zweimal wegen Ulcus duodeni eingebracht war.

Die Ulcushäufigkeit bei Kindern aus diesem kleinem Material zu diskutieren ist unmöglich, aber ich bin geneigt, Forsell Recht zu geben, dass das Leiden häufiger sein kann, als angenommen wird. Donovan u. Santulli sind derselben Meinung.

Da Kinder gewöhnlich keine mustergültige Beschreibung ihrer Symptome liefern können, bekommt man in der Regel nur ein recht monosymptomatisches Bild, das als Kardinalsymptome Magenschmerzen im oberen Teile des Abdomens und Erbrechen hat. Hierzu können verschiedene Symptome kommen, teils charakteristische, teils uncharakteristische für die Ulcusdiagnose. Je älter das Kind ist, desto bessere Auskünfte kann man bekommen und desto sicherer sollte man die Diagnose stellen können.

Über die Ursachen der Ulcuserscheinung gibt es immer viel Uneinigkeit. Meine 3 Fälle von Ulcus ventriculi stammen aus dem Polarland, was möglicherweise in Verbindung mit ernährungsmässigen (8) und klimatischen Verhältnissen (10) steht. Ob die Lokalisation bei diesen 3 Knaben von psychotraumatischer Einwirkung herrührt, will ich nicht entscheiden, da Beweise für eine solche Behauptung fehlen würden.

Zusammenfassung.

Unter 62 Patienten mit Magenbeschwerden, behandelt im Vardöer Krankenhaus (Norwegen) in den Jahren 1945—46, gab es 3 Knaben von 9—10 und 14 Jahren mit Ulcus ventriculi. Dazu kam ein Fall desselben Leidens, beobachtet im Haderslev Stadt-Krankenhaus (Dänemark). In diesem Krankenhaus fand man unter im ganzen 421 Magengeschwürpatienten, 9 Kinder mit Ulcus duodeni im Alter von 7—14 Jahren. Von diesen 9 Kindern waren 5 Knaben und 4 Mädchen.

Nur ein Knabe mit Ulcus ventriculi hatte eine profuse Blutung (starb 23 Jahre später an Hämatemesis nachdem er in der Zwischenzeit symptomfrei gewesen war), während von den übrigen 12 Kindern nur 2 »anamnestische Meläna» hatten.

Da Kinder nur recht monosymptomatische Beschreibungen ihrer Leiden geben können, besteht die Möglichkeit, dass die Ulcuskrankheit bei Kindern häufiger ist, als allgemein angenommen.

Es wird erörtert, dass Kinder im schulpflichtigen Alter einen Symptomenkomplex für Magengeschwür haben, der dem der Erwachsenen ähnlicher ist, als der Symptomkomplex, der bei kleinen Kindern zu finden ist, wo die Blutungen zu dominieren scheinen.

Summary.

Among 62 patients with stomach ulcers treated in the Vardö (Norway) hospital during the years 1945—46, there were 3 boys, aged 9, 10, and 14, with ulcus ventriculi. In addition another case with the same disease from the City Hospital in Haderslev (Denmark) is discussed here. At the last-named hospital there were out of 421 patients with stomach ulcers 9 children aged 9 or 10 with ulcuse duodeni (5 boys and 4 girls). Only 1 boy with ulcus ventriculi had profuse bleeding. (He died 23 years later of hematemesis, after having been free of symptoms during the intervening period). Of the other 12 children, only 2, according to anamnesis, had had melena.

Inasmuch as children can describe their ailments only monosymptomatically, it is possible that they suffer from ulcers more often than is generally assumed. The possibility is discussed that the symptom complex for stomach ulcers in school-age children resembles the symptom complex of adults more closely than that of small children, in the case of whom bleeding seems to dominate.

Résumé.

Parmis 62 patients atteints d'ulcère de l'estomac, soignés à l'hôpital de Vardö (Norvège) en 1945-46 on a trouvé 3 garcons de 9—10 et 14 ans ayant un ulcère de l'estomac. A ceux-là s'ajoute un cas de la même maladie observé à Hôpital de l'Etat de Haderslev (Danemark). A ce dernier hôpital on a trouvé parmi 421 patients atteints d'ulcère de l'estomac, 9 enfants de 9—10 ans ayant un ulcère du duodénum (5 garçons et 4 filles). Seul un de ces

enfants avait des hémorragies profuses. (Il est mort 23 ans plus tard d'hématémèse, après avoir été exempt de symptômes durant l'époque intermédiaire). Parmi les 12 autres enfants, 2 seulement, d'après l'histoire de la maladie, ont eu le mélaena.

Comme les enfants ne peuvent décrire leurs douleurs que d'une manière monosymptômatique il est possible qu'ils aient des ulcères plus souvent qu'on ne le suppose. On se demande si l'ensemble des symptômes d'un ulcère de l'estomac chez les enfants à l'âge d'aller à l'école, ressemble davantage à l'ensemble des symptômes chez les adultes qu'à ceux des petits enfants chez lesquels les hémorragies semblent dominer.

Resumen.

Entre los 62 enfermos de ulceración atendidos en el hospital de Vardö (Noruega), en 1945—46, había 3 muchachos de 9—10 y 14 años con ulcus ventricular. A éstos hay que agregar otro caso observado en el hospital de Haderslev (Dinamarca). En este hospital había, entre 421 enfermos de ulceración, 9 niños de 9—10 años (5 varones y 4 hembras) con ulcus duodenal. Sólo un muchacho con ulcus ventricular tuvo una hemorragia profusa (murió 23 años más tarde de hematemesis, sin haber presentado síntomas durante el tiempo intermedio). De los otros 12 niños sólo 2 habían tenido, según la anamnesia, melena. Como que los niños sólo pueden describir sus sufrimientos monosintomáticamente, es posible que las enfermedades de ulcus sean en ellos más frecuentes que lo que se cree. Se discute la posibilidad de que las combinaciones de síntomas de ulceración en niños de edad escolar se parezcan más a las de adultos que a las de los niños en los cuales dominan las hemorragias.

Litteratur.

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FROM KRONPRINSESSAN LOVISAS BARNSJUKHUS, STOCKHOLM, SWEDEN.
CHIEF: PROFESSOR A. LICHTENSTEIN, M. D.

Heart Index or Heart Volume in Judgement of Congenital Heart Diseases.

By

SIGURD EEK

Oslo.

Authors in many countries have tried to measure the size of the heart. Since there is no agreement on the most useful and most correct method, various calculations are used in different parts of the world. My impression is that in the Anglo-Saxon countries »the cardiac-thoracic ratio or heart index» is most common, while in Scandinavia, especially in Sweden, the preferred method is volume determination according to Rohrer-Kahlstorf's formula for elipsoid bodies.

In this clinic S. Jonsell's modification of the Rohrer-Kahlstorf formula is used, $K \times L \times B \times D$. K is a constant of several factors, among others the focal distance, L or the longest diameter is measured from the base of the shadow of the arterial trunk on the right side of the heart down to the apex. B or the broadest diameter is the shortest distance from the right heart-diaphragmatic angle to the left border of the heart. The third measurement (D) is the greatest depth from the frontal border of a moderately filled esophagus to the frontal border of the heart, or, if this is not definable, to the posterior border of the sternum.

In patients examined in erect position with a focal distance of 1.5 m, K is .42. In patients in supine position with a focal distance of .90 m the constant K is .33. In order to obtain comparable data, the volume figure expressed in cc is transferred into cc per square meter of body surface according to Du Bois' formula.

This heart-volume determination method can be used for

patients of all age groups, even infants, as shown by AXÉN and LIND. Table 1 is taken from their work and shows good agreement between postmortem X-ray examination and direct measurement of the volume of the heart at autopsi.

Fig. 1.

Heart volume determined roentgenogically after death (in cc)	Heart volume measured at autopsy (Displacement) (in cc)
38	40
65	65
84	75
120	120
106	105

Up to now complete figures for some age groups in childhood have been lacking, but they are at present being worked out by J. LIND. I am using data given in the forementioned paper by AXÉN and LIND for infants and by CARLGREN for the age groups 4—7, 9—12, and 14 to 16.

Table 2 shows that there is a uniform increase in heart volume per square meter of body surface from the first month of life equal to 196 ± 26.6 cc, until the age group of 14—16 years when it equals 398 ± 61.9 cc. The figures given are means and standard errors of the mean. Up to the present there have not been enough cases available to permit determination of the normal variation. Fig. 2.

Fig. 2.

Age	Heart volume p:r square m. body surface	Standard error of the mean
0— 30 days	196.0 cc	± 26.6
30— 90 ,,	217.8 ,,	± 33.9
90—360 ,,	282.0 ,,	± 35.8
4— 7 years	310.0 ,,	± 36.2
9—12 ,,	348.7 ,,	± 33.6
14—16 ,,	398.0 ,,	± 61.9

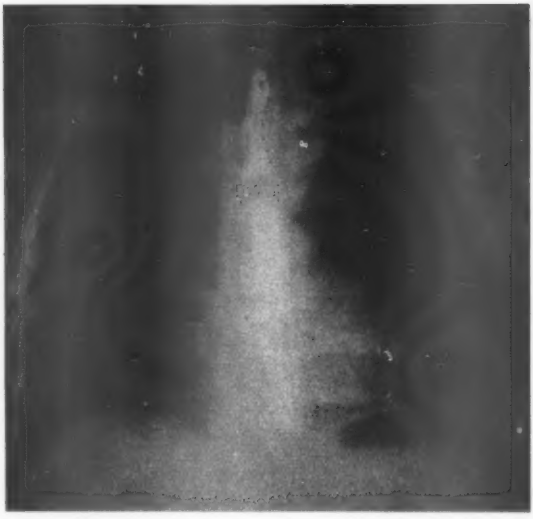

Fig. 3.

The heart index increases in healthy infants from .55 at birth to .58 at the end of the first year. Later on it falls rapidly down to .45 at 2 years of age. After this age group the figures remain fairly constant (.44 at 12—14 years of age). (BAKWIN and BAKWIN, MARESH and WASHBURN, LINCOLN and SPILLMAN.)

This short survey includes only cases of Fallot's tetrad and Eisenmenger's complex.

The 23 cases of Fallot's tetrad, 15 boys and 8 girls, had an average age equal to $5^{7}/_{12}$ years. The heart index varied between .45 and .69, averaging .55. The heart volume per square meter of body surface varied between 160 cc and 745 cc, averaging 370 cc.

In addition 7 cases of Eisenmenger's complex were examined, 4 boys and 3 girls, with an average age of $8^{8}/_{12}$ years. The heart index varied between .44 and .62, averaging .54. The heart volume per square meter of body surface varied between 415 cc and 770 cc, averaging 550 cc.

In spite of the fact that the Eisenmenger cases were on the

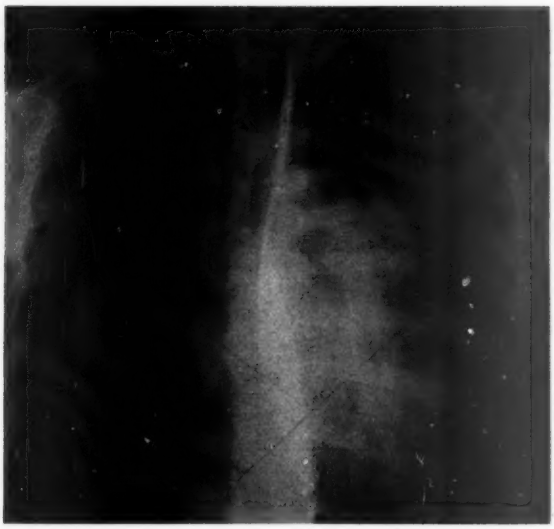

Fig. 4.

average 3 years older than the Fallot cases, there is no real explanation of the incongruity between the results of the index and volume determinations. There is practically the same heart index in both groups, .55 and .54 respectively. The volume figures are 370 cc in the Fallot group but 550 cc in the Eisenmenger group.

The simplest way to explain this incongruity between index and volume is to compare the X-ray of a Fallot case with that of an Eisenmenger patient. I have chosen two patients with nearly the same index, .55 and .54, the average of each group.

Fig. 3 gives the X-ray of the Fallot case and Fig. 4 that of the Eisenmenger patient. They were about the same age and size.

If the two X-rays are projected on top of one another the picture in Fig. 5 will be obtained.

The dotted line indicates the Fallot heart and the uninterrupted line the Eisenmenger heart. The heart index is about the same in both cases, .55 and .54 respectively, and the heart volume 385 cc and 770 cc per square meter body surface. It will be noted that

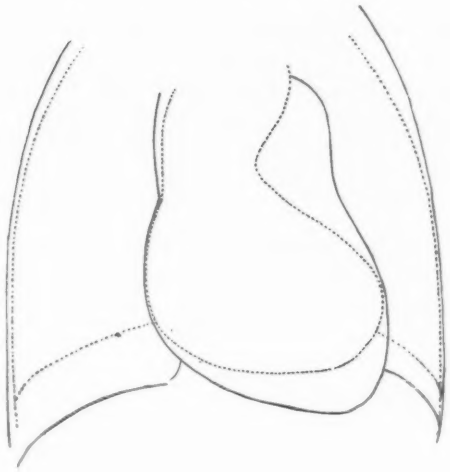

Fig. 5.

the Fallot heart is much smaller than the Eisenmenger heart. This is due to the fact that the base of the heart in the Fallot case is much narrower and does not reach down as deeply as the other. Furthermore, the markedly transverse position of the Fallot heart plays an important role as far as the index figure is concerned. If the main axis of this heart was in a normal position, with the apex turned down, the result would have been a shorter transverse diameter and a considerably smaller index.

If the X-rays are projected in the same way in lateral position as in Fig. 6, the difference in size is obvious. The Eisenmenger heart bulges much more posteriorly, and reachs considerably farther down. The main objection to the heart index method seems to me to be that it leaves the investigator in ignorance of the depth of the heart.

It must be emphasized that the volume method according to JONSELL cannot pass as a mathematical expression of heart volume. The heart is not an exact elipsoid body. Furthermore, such factors as the heart and respiration are of some importance phases in the moment of exposure, the pulse frequency, and the

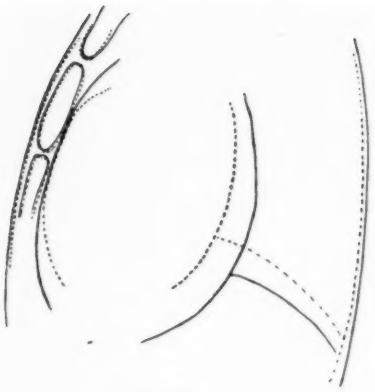

Fig. 6.

patient's position (erect or supine). Jonsell also emphasizes these facts, and he calls the figures obtained by this method heart volume figures.

The majority of these factors also affect the calculation of the heart index. But from a practical point of view these sources of error are of little consequence. The heart volume method is easy to handle, and in my opinion should be used as a matter of routine since it gives relatively correct information concerning the size of the heart in both normal and pathological cases.

Summary.

The author shows by determining the size of the heart, that the heart volume method according to S. Jonsell is superior to the heart index method. 23 cases of Fallot's tetrad and 7 of Eisenmenger's complex are compared. Projection of a Fallot X-ray on top of that of an Eisenmenger patient shows that the heart index method does not take into consideration the depth or length of the heart and thus gives a very inexact indication of its size.

Résumé.

L'auteur montre que dans la détermination du volume du coeur, la méthode S. Jonsell est supérieure à la méthode index.

23 cas de tétralogie de Fallot et 7 cas de complexe Eisenmenger sont comparés. En projetant une radiographie d'un patient de Fallot sur celle d'un Eisenmenger on constate que la méthode index ne tient pas compte de la profondeur ou de la longueur du coeur et ne donne donc nullement une notion exacte de son volume.

Zusammenfassung.

Bei der Bestimmung der Grösse des Herzens fand der Autor, dass die Herz-Volumen-Methode nach S. Jonsell der Herz-Index-Methode überlegen ist. 23 Fälle von Fallot's Tetrade und 7 Fälle von Eisenmengers Komplex wurden verglichen. Bei der Projektion eines Röntgenbildes eines Fallot-Patienten genau über das eines Eisenmenger wurde gefunden, dass die Herz-Index-Methode die Tiefe und Länge des Herzens nicht berücksichtigt und in keiner Weise einen genauen Ausdruck seiner Grösse gibt.

Resumen.

Por la determinación del tamaño del corazón el autor demuestra que el método de determinación del volumen del corazón ad modum S. Jonsell es superior al método índice. Se comparan 23 casos de tetralogía de Fallot y 7 de complejos de Eisenmenger. Proyectando una radiografía de un paciente de Fallot sobre uno de Eisenmenger se comprueba que el método índice no toma en consideración la profundidad y la longitud del corazón y que por lo tanto no da una expresión exacta de su tamaño.

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FROM THE CHILDREN'S CLINIC AND THE DEPARTMENT OF PHYSIOLOGY, UNIVERSITY OF HELSINKI.

Absence of Fructose from Human Cord Blood.

By

M. J. KARVONEN.

The amniotic fluid of some animal species is known to give a positive SELIWANOFF (1887) reaction. Seliwanoff's test is used as a reaction for fructose, but it also gives a positive result with all other ketoses and inulin (BARCROFT, 1946). Recently, however, BACON & BELL (1947) have been able to isolate and identify fructose from the fetal blood of sheep. In addition, the analyses of COLE & HITCHCOCK (1946) and of HITCHCOCK (1948) indicate that a rather substantial portion of the blood sugar of fetal sheep is made up of fructose.

These investigations and the reported presence of fructose in human amniotic fluid (IZITYÔ, 1934) made it desirable to re-examine human fetal blood with the object of investigating the presence or absence of fructose. The present paper gives an account of analyses of human cord blood carried out with the technique developed by COLE (1946).

Material and Methods.

The *material* of the present work consists of 30 samples of human cord blood obtained in the course of normal deliveries. The birth weights of the babies varied from 2.240 to 5.140 g (average 3.470 g). The samples were taken in bottles containing 10 to 20 mg solid sodium fluoride per cc blood and were immediately placed in a refrigerator. *Protein precipitation* was carried out according to the method of FUJITA & IWATAKE (1931). In the

protein-free filtrate the *total blood sugar* was determined according to Somogyi's titrimetric method (1945), using 1 or 2 cc blood samples. When enough blood was available, triplicate determinations were made. The agreement between the individual titration values was very close. For *fructose* determinations, Cole's modification of Roe's colorimetric method (1934, based on Seliwanoff's reaction) was used. Instead of a photoelectric colorimeter, a Pulfrich photometer (filter S 50, optic depth 30 mm) was used for the colour measurements. A fructose determination as made on distilled water was used on the comparison side of the photometer. Blank and control titrations and colorimetric analyses were performed daily.

The samples collected during a night were analysed on the following morning. Thus on the average the samples were examined $9^1/_2$ hours after being taken. The effect of *keeping the samples* was tested in 5 cases. The blood sugar analysis was carried out immediately after sampling and again 22 to 28 hours afterwards. The results are compiled in Table 1. They indicate that in spite of the addition of fluoride, some glycolysis occurs in cord blood. The total sugar values obtained in the present work are therefore probably slightly lower than they would have been if all the samples had been examined immediately.

Table 1.

Subject	Total Immediate Sugar	No. Hours preserved	Final total Sugar
E. L.	86	28	53
M. K.	102	28	85
H.	93	27	67
G. W.	81	22	67
T.	82	22	72

When varying amounts of fructose were added to human adult or cord blood, *recovery* with Somogyi's method was 91 % to 108 % and with Cole's method 98 % to 110 %. In fluoride blood the fructose was quite stable. No conversion to glucose could be observed in samples preserved for 24 hours.

Fermentation experiments were performed on 5 samples of oxalated cord blood. The proteins were removed in the usual way. One volume of a 1:5 suspension of well-washed baker's yeast was made in 0.9 % NaCl. The yeast was centrifugalized and the precipitate mixed with one volume of the protein-free filtrate. The mixture was incubated for 12 minutes at 37° C. It was then centrifugalized sharply with some added kieselguhr, and the supernatant fluid was collected for sugar determinations. The reduction disappeared in all samples investigated. Thus the results of the application of Somogyi's method to human cord blood indicate concentrations of fermentable substance only.

Results.

In 3 of the 30 samples of cord blood, fructose analysis indicated 1 mg-% fructose. In the remaining 27 samples, the photometer-reading was equal to that obtained when using distilled water. Values like 1 mg-% must be regarded as falling within the limits of the methodical error. Therefore the conclusion may be drawn, that at birth human cord blood contains less than 1 mg-% fructose, if any at all.

The values for total sugar varied between 36 and 116 mg-%. The average and its standard deviation was 78 $\pm$ 28 mg-%. (The average of the 5 samples investigated immediately was 89 mg-%.)

Discussion.

Great differences are known to prevail in the carbohydrate metabolism of different mammalian species. The same seems to be true of the carbohydrates of the fetus. The concentration of fructose in the fetal blood of sheep remains high until delivery, whereafter it rapidly disappears. In man, however, there is practically no fructose in the blood at birth. It still remains to be shown whether any fructose can be found in the blood of younger human fetuses.

Summary.

30 samples of human umbilical cord blood (the birth weights of the babies varied from 2.240 to 5.140 g) were examined with the object of ascertaining the presence or absence of fructose, using Cole's method. In 3 samples 1 mg-% fructose was found; in the rest no positive reaction was observed. The total (fermentable) sugar values as determined with Somogyi's method varied between 36 and 116 mg-%.

Résumé.

30 exemplaires de sang du cordon ombilical humain (le poids des nouveau-nés variait de 2.240 à 5.140 g) ont été examinés par la méthode Cole, au sujet de la présence ou l'absence de fructose. Dans 3 exemplaires on a trouvé 1 mg %, dans les autres on n'a constaté aucune réaction positive. La valeur totale de sucre (fermentable) déterminée par la méthode Somogyi variait entre 36 et 116 mg %.

Zusammenfassung.

Es wurden 30 Proben von Nabelstrangsblut (das Geburtsgewicht der Kinder variierte von 2.240—5.140 g) nach Cole's Methode untersucht, um das Vorhandensein oder Fehlen von Fruktose nachzuweisen. In 3 Proben fand man 1 mg-%, die übrigen ergaben keine positive Reaktion. Die totalen (vergärbaren) nach Somogyi's Methode bestimmten Zuckerwerte schwankten zwischen 36 bis 116 mg-%.

Resumen.

Mediante el método de Cole se examinaron 30 muestras de sangre del cordón umbilical (los pesos de nacimiento de los niños varían entre 2.240 y 5.140 g) para determinar la presencia de fructosa. En tres muestras se encontró un milígramo por ciento y en las restantes no se observó ninguna reacción positiva. Los valores totales de azúcar (fermentable) varían entre 36 y 116 milígramos por ciento, determinados según el método de Somogyi.

The author wishes to express his deep gratitude to Prof. A. Ylppö, M. D. and Dr. C.-E. Räihä, of The Children's Clinic, for their interest in the present work; to Prof. M. Rauramo, M. D., for allowing him to collect blood samples from his clinic; and to Miss Eila Ala-Ketola, who has performed all the sugar analyses. A grant has been obtained from »Lastentautien Tutkimusrahasto» (Foundation for the Investigation of Children's Diseases).

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(FROM THE STATE HOSPITAL, COPENHAGEN, PEDIATRIC DEPARTMENT.
CHIEF: PROFESSOR P. PLUM, M. D.)

On the Cause of Familial Deaths in Early Childhood, with Particular Reference to Some Uncommon Conditions.

By

HJALMAR WERGELAND.

Improved hygiene and prophylaxis have perceptibly reduced infant mortality in most countries, not least in Scandinavia, during the last decades. In fact, infant mortality has gradually fallen so low that several deaths among siblings are bound to attract attention, especially since what was formerly the most common cause — congenital syphilis — has been removed to a considerable extent by means of effective prophylaxis and treatment.

In the course of the last 3 years a number of deaths among siblings have been observed at the Pediatric Department of the State Hospital (P. D. S. H.). The unusual conditions surrounding these deaths have been reported at the meetings of the Society of Danish Pediatricians and will probably be published in more detail elsewhere. Therefore they will be mentioned here only briefly.

(1) The most common cause of deaths among siblings in early childhood is *erythroblastosis foetalis* (e. f.). The pathogenesis of this disease and the cause of its familial occurrence must be considered so wellknown that further explanations are superfluous. During the last 2 $^1/_2$ years a total of 28 cases have been treated at P. D. S. H. In 3 of these cases the family history was incomplete. Among the remaining 25 there was familial occurrence and death in 19 (abortions being included in the deaths). In 14 of these families there was 1 death, in 3 there were 3, and in 2 there were 4. In 2 of these 25 families, e. f. occurred as early as after

the 1st pregnancy without a previous blood transfusion to the mother. In 2 additional families the 1st pregnancy ended in abortion and the 2nd in e. f. There may be some doubt as to whether the abortion was caused by e. f. or something else. The same applies to other cases in which an abortion was followed by a case of e. f. after one or several normal pregnancies. Leaving such abortions out of account, the figures are as follows:

14 cases of familial occurrence, in 11 of which there was 1 death: 1 case of 3 deaths; 1 case of 4 deaths.

The constellation Rh− mother/Rh+ child is seen in about every 25th birth, whereas e. f. occurs only once in every 200—300 births. In addition to the blood groups, other factors must play a rôle. In view of the familial occurrence of e. f. WIENER has concluded that a familial predisposition is required for its development. Our material comprised only one case where there was further familial occurrence (the mother's sister had lost 4 children with e. f.).

(2) *Congenital Cystic Fibrosis of the Pancreas*

This disease gives rise to a syndrome which previously was often misinterpreted, but which is now being diagnosed with increasing frequency. It is characteristic that the 5 cases observed at P. D. S. H. date from the last 3 years and that the diagnosis was made *ante mortem* in merely 2 of the cases. In all the cases the autopsy findings were negative with regard to the pancreas on first inspection. It was only revision of the microscopic preparations undertaken because of a suspicion of pancreatic fibrosis that afforded the diagnosis.

The 5 cases (reported before the Society of Danish Pediatricians by E. WINGE FLENSBORG) represent the various clinical forms of pancreatic fibrosis. (a) 2 cases revealed symptoms of intestinal obstruction right from birth. Autopsy showed meconium ileus. (b) At the age of 6 weeks 2 of the cases exhibited symptoms of pulmonary disease combined with chronic dyspepsia in the form of frequent, voluminous, fatty and foul-smelling stools and failure to thrive. The infants died at 3 months with marked pulmonary symptoms. (c) At the age of 3 months 1 case exhibited a similar

dyspepsia and dystrophy which gradually grew more like celiac disease. From the age of 6 months there was a productive cough, febrile periods, and auscultatory signs of bronchopneumonia. Death followed at the age of 11 months.

One of these 5 cases had a family history, with a sister who died at the age of 2 months after having exhibited dyspepsia and pulmonary symptoms from birth and another sister now in the hospital for the same disease.

(3) *Cirrhosis of the Liver*

Cirrhosis of the liver in childhood is not uncommon, and its clinical features differ from those of the adult condition only in that the onset is more acute and the course more rapid.

Familial cirrhosis of the liver can very seldom be traced to previous generations, but is comparatively often encountered among siblings. The literature contains quite a number of such reports. Several of the cases reported were secondary forms, partly amenable to treatment, but most of them belonged to the idiopathic group in which treatment is purely palliative. This »juvenile familial cirrhosis» is, however, relatively rare, and only in India and certain parts of Mexico is it said to be of common occurrence.

In order to find a basis for a causal therapy it is important to decide whether each particular case of cirrhosis belongs to the idiopathic or secondary form. The following table, comprising the secondary forms, sets out the types of cases within this group which may be presumed to be of familial occurrence and indicates whether or not these have been found in the literature.

If upon clinical examination these secondary forms of cirrhosis of the liver may be ruled out, it must be assumed that it is a question of the idiopathic form.

Writer's Cases. (Reported by WAMBERG before the Society of Danish Pediatricians, 1947.)

Three siblings. Parents and all children Rh+ (no agglutinins in the mother's serum), Wassermann reaction negative. All three children normal at birth. Breast-fed. At the age from 3—6 weeks

Cause	Familial Occurrence Imaginable	Familial Occurrence Reported
I. *Obstruction of Bile Ducts*		
(a) Congenital malformations		
Atresia of bile ducts	×	
Cysts in common duct and idiopathic dilatation	×	
(b) Cholelithiasis combined with hæmolytic jaundice	×	
(c) Indurated plug of bile co-existing with infection in pancreatic fibrosis	×	
Erythroblastosis foetalis	×	
II. *Congestive Cirrhosis*		
(a) Heart failure (particularly pericarditis)		
(b) Thrombophlebitis in the vena cava		
III. *Infection*		
(a) Sepsis		
(b) Congenital syphilis	×	× Poynton & Wyllie, Schusik
(c) Acute hepatitis		
(d) Tuberculosis	×	? Glanzman
(e) Other infectious diseases (sequel of whooping cough, scarlet fever, measles)	×	× Moon
IV. *Intoxications*		
(a) Alcohol	×	× Schusik
(b) Other medicaments (*int. al.* arsenic)	×	
V. *Congenital malformation of the liver*		
Hereditary angiomatosis	×	× Nelson & Mitchell, p. 675
VI. *Parasitosis*		
Malaria, kala-azar, ascaris	×	× Tucker, Duprey, Rogers
Hydatid cyst	×	

They all exhibited symptoms of hepatic disease, i. e. jaundice, hepatomegalia, anemia, bile pigments in the urine, and 2 of them also had hemorrhagic diathesis with subarachnoid hemorrhage, from which one died at 7 weeks of age (autopsy: no signs of cirrhosis of the liver). The other 2, on the other hand, then had a period of about 1 year of complete freedom from symptoms apart from enlargement of the liver — whereupon they again for a time showed all signs of obstruction of the bile ducts. From the eldest child a biopsy specimen was obtained from the liver. It showed »initial cirrhosis». Both patients gave a negative reaction to Takata-Ara; there was no ascites or enlargement of the spleen. In a few weeks all the symptoms again subsided with the exception of the hepatomegalia, which remained unchanged. At the present time the youngest child is at this stage of the disease ($1\,^3/_4$ years of age). In the case of the eldest child symptomless periods of several months up to a year went on alternating with bouts of jaundice and other signs of biliary obstruction. From the age of 4 there was beginning enlargement of the spleen and from the age of $4\,^1/_2$ beginning ascites. It was not until this point that Takata-Ara was positive. There again followed a period during which the symptoms subsided, but at the age of 5 there was again exacerbation. This time the ascites was so severe that Talma's operation was performed. The laparotomy revealed marked enlargement of the liver and spleen. Thereafter there was increasing ascites and exacerbation of the general condition. Death followed at the age of $5\,^1/_2$ years. Autopsy was not allowed.

In these cases it was impossible to find any primary disease, for which reason they have been interpreted as cases of »juvenile familial cirrhosis».

(4) *Malrotation of the Intestine*

This disease is due to a change in the normal development of the position of the colon and the attachments of the mesentery in the abdominal cavity. The cecum remains close to the liver, while remnants of its mesentery run like a ribbon across the descending part of the duodenum. At the same time the attach-

ment of the mesentery of the small intestine to the posterior abdominal wall is often very narrow and this involves the risk of volvulus. As a rule the symptoms are indications of intermittent, high-seated intestinal stenosis (not unlike pyloric stenosis), or perhaps complete stenosis with a rapid course (volvulus). Familial occurrence of this condition does not appear to have been reported in the literature.

In the P. D. S. H. the following cases have been observed (briefly reported by WINKEL SMITH at a meeting of the Society of Danish Pediatricians in 1947).

The parents, who have always been healthy, have had 7 children with histories briefly as follows:

No. 1. Born prematurely, weight 1 500 g, died in a few days. No vomiting.

No. 2. Weight at birth 2 500 g. Frequent vomiting during the first year, later well.

No. 3. Born 7 weeks before term, weight 2 500 g. Daily vomitings, not containing bile pigment, not explosive (exactly like our patient, No. 7). Hospitalized for 2 $^1/_2$ months and had at last attained a weight of 4 500 g when death occurred at the age of 9 months from an intercurrent infection.

No. 4. Weight at birth 3 500 g. Healthy up to the age of 7 years, later suffering from frequent attacks of colic.

No. 5. Born 8 weeks before term, weight 2 500 g. Vomiting right from birth like No. 3. A period of perfect health, then again vomiting. Died at 5 months from pneumonia.

No. 6. Weight at birth 2 500 g. Breast-fed up to 1 year of age, in perfect health. Suddenly one day violent vomiting and abdominal pain but no fever. Died after 24 hours exhibiting symptoms of intestinal obstruction.

No. 7. Weight at birth 3 500 g. Right from birth spitting and vomiting, partly explosive. As marked gastric peristalsis was seen, a diagnosis of pyloric stenosis was made at P. D. S. H. and the baby operated upon. The operation revealed malrotation of the intestine and ribbon-shaped adhesions running across the descending part of the duodenum. Marked improvement after the operation, but 6 weeks later the symptoms of stenosis recurred and death ensued in a short time. Autopsy revealed jejunal volvulus (as well as coarctation of the aorta and patent ductus arteriosus).

It is impossible to prove that the 3 children who died earlier also suffered from malrotation, but according to the mother the

symptoms in Nos. 3 and 5 were exactly like those exhibited by our patient, and the course of the disease in No. 6 is extremely indicative of volvulus.

(5) *Allergy*

Allergic diseases in children are wellknown, particularly allergy to cow's milk. Allergy to human milk has also been reported — usually in the form of a benign diarrhea, due mainly to greatly increased peristalsis. The prognosis of this condition is not always favourable, as is apparent from the reports of a few cases ending fatally because of anaphylactic shock and the following cases reported by the author before the Society of Danish Pediatricians in 1948.

Recently 3 siblings suffering from allergy to, among other things, human milk, were treated at the P. D. S. H. The symptoms were diarrhea present from birth in the form of frequent, squirting, loose, not foul-smelling stools, and failure to thrive in spite of ravenous appetite. Two of the children exhibited eczematous eruptions. The first 2 cases followed a downhill course in spite of every conceivable treatment and died in the course of 2—3 months after mild infections. The 3rd case was eventually treated with »soya milk», whereupon all the symptoms subsided and there was distinct improvement — until a fortnight later, when the patient had an allergic shock which, however, could be relieved. Subsequent treatment with amino acids administered intravenously appeared to have a good effect, but one day the patient suddenly died of pulmonary edema.

In these cases there were no signs of other disease which might explain the symptoms; there was thus neither pancreatic fibrosis nor infection. The post-mortem examinations failed to give any explanation. On the other hand there were several signs of allergic diathesis, including, apart from the eczema, definite indications of idiosyncrasy to cow's milk and, after a fortnight's soya milk treatment, allergy to soya also.

(6) *Cerebral Hemangioma*

In December, 1947, a patient was transferred from the Department of Neurosurgery to P. D. S. H. as suffering from »atro-

phic cerebral affection with attacks due to lesion of the brain stem».

The child's parents were not related. There was no family history of diffuse cerebral sclerosis, but the paternal grandmother suffered from a disease described as cerebral asthenia and there had been several cases of unelucidated insanity and narcomania in the father's family, in which there were also several intermarriages. The first child had been normal at birth, but the delivery had been difficult. At the age of about 1 month he began to show signs of rigidity in the trunk and limbs and had a few contractions. Spinal fluid normal; Wassermann reaction negative. Gradually he developed seizures of clonic convulsions in the limbs and exhibited a typical picture of diffuse cerebral sclerosis of the familial progressive form (Krabbe) with atrophy of the optic nerves. — He died at home from pneumonia at the age of 7 months. Autopsy not performed.

Child No. 2 — our patient — was born at term. Delivery was again rather difficult. At the age of 14 days he began to have contractions, later convulsions, in the arms and to suffer from increasing rigidity. These phenomena persisted and he had 1—4 seizures daily, unaffected by phenemal. He was admitted to the Department of Neurosurgery where the following examinations were made, among others: bilateral puncture of the fontanelles by the method of Ingraham: clear fluid; X-ray of the skull: natural; ophthalm. exam.: deep excavations into both optic disks, which were pale on the temporal aspect (presumably physiological excavation). This last gave no indication for surgical intervention. — On account of persistent fever the patient was transferred to P. D. S. H. where, in addition to the symptoms described above, signs were observed of a pulmonary disease which proved refractory to treatment. Death followed after the lapse of a week. At autopsy no signs could be found of cerebral sclerosis, but in the pons in the region of the corticospinal tract there was an angioma as large as the head of a pin surrounded by congestion and perivascular hemorrhages of older as well as more recent date.

If no autopsy had been performed in the latter case, the condition would have been interpreted as cerebral sclerosis as in the

case of the brother. Apart from the ophthalmological findings, the symptoms were almost identical, and the disease is known to be familial. Cerebral angiomas have also been described in siblings, and considering that the diagnosis of diffuse cerebral sclerosis has not been verified, it is warrantable to wonder whether this too was not actually a cerebral angioma or whether this is a case of 2 different familial lesions within the same family.

(7) *Spinal Progressive Myopathy*

This disease is met with in various forms of which one — the infantile type (Werdnig-Hoffmann disease) — is recessive and comparatively often found among siblings. It usually occurs during the 1st year of life and is often present right from birth. The prognosis is very poor — the patient usually dying before reaching the age of 2 of pneumonia (respiratory paresis).

At the P. D. S. H. 1 case of this disease with familial occurrence has been observed. The first child was healthy, No. 2 was still-born, and No. 3 died at 3 $^1/_2$ months from »wasting of the muscles» and pneumonia. No. 4 — our patient — exhibited weakness of the muscles only a few days after birth. Gradually he developed muscular atrophies and pareses and died at 5 months. Autopsy showed »spinal muscular dystrophy».

With regard to differential diagnosis it is important to distinguish the disease from benign amyotonia (Oppenheim's disease). The main criterion is that Oppenheim's disease is never attended with pareses or muscular atrophy and that Werdnig-Hoffmann disease progresses, whereas the symptoms of Oppenheim's disease remain stationary or abate.

(8) *Spina Bifida Aperta*

This is a fairly common disease — according to KEMP it occurs in 1 out of every 1 000 births — and often co-exists with other malformations. It is considered to be recessive.

In March 1948 P. D. S. H. received a patient, aged 14 days, with an infected urachal fistula. The child was the youngest of a family of 3 and both elder siblings had died of spina bifida aperta.

(9) *Gaucher's Disease*

This disease, which is grouped with lipoidoses, in some cases shows recessive heredity and is now and then encountered in siblings. Unlike adults, children usually exhibit the acute form. The main symptoms are neurological in combination with progressive cachexia and a large abdomen (enlargement of the liver and spleen caused by a pathological accumulation of cerebrosides). The prognosis is poor, death occurring in the 1st or 2nd year of life.

The writer knows a family who lost one child from Gaucher's disease which has now been diagnosed in child No. 2. As the patient has not been admitted to the P. D. S. H. the case will not be dealt with further.

(10) *Unknown Cause (Tetanus of the Newborn)*

A brief report will be given of the following peculiar case:

The patient's maternal grandmother lost 4 children of tender years — no symptoms stated. This grandmother's brother had 5 children, of whom 4 died at the age of 2 to 4 weeks with the same symptoms as our patient. At the ages of 3 and 6 weeks child No. 5 had the same kind of attacks as our patient, but recovered and is still alive and in good health at the age of 2 years.

The patient is the youngest of a family of 3. The first 2 children died at 2 and 14 days respectively exhibiting the same symptoms as our patient. The latter was born at term and the delivery was natural and easy. He was mainly breast-fed and developed normally up to the age of 20 days, when he suddenly had an attack of cyanosis with weak, shallow breathing and severe weakness. Following subcutaneous administration of stimulants and vitamin K the attack subsided, but recurred at 4—6 hour intervals during the next 36 hours. Each time stimulants were given with a good effect. — On admission the patient was weak, with shallow breathing and rapid heart beats, some rigidity of the left extremities, and firmly closed fists. There were slight contractions in the face and upper limbs, but no convulsions. Chvostek —, Trousseau —. Shortly after admission he had another attack manifesting

itself in the form of severe cyanosis, markedly stridulous respiration, and extremely irregular heart beats (50—170). Following artificial respiration, oxygen, and stimulants he recovered in the course of 5 minutes. Renewed attacks half an hour and 2 hours later. Because of a suspicion of tetanus he was now given an intramuscular injection of calcium gluconate (10 per cent.), 3 cc. During the injection he had a new attack of cyanosis and half an hour later an approach to an attack which, however, subsided spontaneously. After that there were no attacks. On the following day he also received calcium (5 cc) — and thereupon no further medicaments. In the course of about 1 week he was quite all right again.

The various examinations afforded no basis for a diagnosis. Spinal fluid was normal and Wassermann reaction negative. X-ray of heart, lungs and trachea: normal. Urine: normal. Because of a regrettable error in the method of analysis the determination of calcium in the blood — in this case the decisive test — became worthless. In view of the family history, the stridulous respiration, and the apparent temporary curative effect of calcium, the diagnosis of tetanus neonatorum must, however, be considered the most likely one.

These are the diseases causing familial infant mortality met with at the P. D. S. H. in the course of the last 3 years. Such cases often represent difficult problems of diagnosis. It might therefore be interesting to have a survey of the diseases worth considering in this respect. The following table[1] comprises only congenital diseases, as acquired environmental diseases like tuberculosis and other infections occurring among siblings can hardly be called hereditary in the strict sense of the word. The references only include papers reporting *familial occurrence*.

[1] The table has been perused and sanctioned by Professor TAGE KEMP, M. D., Chief of the Institute for Human Genetics, Copenhagen, to whom my thanks are due.

Diseases Which May Lead to Death Among Siblings in Early Childhood.

Disease	Heredity	Literature
I. *Congenital Malformations*		
Spina bifida aperta	recess.	1.10.23
Chondrodystrophia	domin.	1.22
Congenital cystic kindney	domin.	1
Malrotation of the intestine	?	Present paper
II. *Diseases of the Central Nervous System*		
Tumors: Glioma	irreg. dom.	1
Tuberous sclerosis	»	1.8
Hemangioblastoma & hemangioma	domin.	1.14
Abiotrophy: Spinal progressive myopathy (Werdnig-Hoffmann)	recess.	1.8.12 b
Krabbe's cerebral sclerosis	»	1.12 a
Niemann-Picks disease	»	1.8
Gaucher's disease	domin. ?	1.8.16
Glycogenosis (v. Gierke)	recess.	5.15
Amaurotic idiocy (Tay-Sachs)	»	1.8.21
III. *Blood Diseases*		
Hemophilia	»	1.4
Thrombopenia	domin. ?	1.27
Hemolytic jaundice	domin.	1.2.6.19.28
Erythroblastosis foetalis	?	
IV. *Digestive and Renal System*		
Juvenile cirrhosis of the liver	recess.	1
Cystic fibrosis of the pancreas		29
Hypernephroma		1.3.7
V. *Endocrine System*		
Diabetes mellitus (in the mother)		18
Hypoparathyroidism		Present paper
Hypothyroidism		18
VI. *Skin Diseases*		
Ichthyosis	recess.	1
VII. *Allergic Disease*		25. Present paper
VIII. *Infections*		
Congenital syphilis		
Toxoplasmosis ?		

Summary.

The writer mentions a number of diseases which may cause familial deaths in early childhood and reports the cases — a total of 10 — observed in the Pediatric Department of the State Hospital, Copenhagen, in the course of the last 3 years.

At the end of the paper the writer sets out in tabular form all the diseases which he has found described in the literature as causes of early familial deaths.

Résumé.

L'auteur mentionne un nombre de maladies qui peuvent causer la mort familiale dans la prime enfance, il rapporte les cas — au total de 10 — observés à la section de Pédiatrie de l'Hôpital de l'Etat à Copenhague au cours des 3 dernières années. A la fin de l'article l'auteur donne sous forme de tableau toutes les maladies qu'il a trouvé décrites dans la littérature comme causes de mort familiale prématurée.

Zusammenfassung.

Der Verfasser erwähnt eine Anzahl Krankheiten, welche familienweise Todesfälle in früher Kindheit verursachen können und berichtet die Fälle — im Ganzen 10 — die in der pädiatrischen Abteilung des staatlichen Hospitals Kopenhagen in den letzten 3 Jahren beobachtet wurden. Zum Schluss stellt er in Tabellenform alle Krankheiten zusammen, die er in der Literatur als Ursache familiärer frühzeitiger Todesfälle beschrieben fand.

Resumen.

El autor describe cierto número de enfermedades que en la primera infancia pueden causar fallecimientos dentro de una misma familia e informa sobre los casos — en total diez — observados en la Sección Pediátrica del Hospital del Estado en Copenhagen durante los últimos tres años. Al final del informe el autor expone en un cuadro todas las enfermedades que ha encontrado en la literatura médica como causantes de fallecimientos en la primera infancia y dentro de una misma familia.

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CASE REPORT

Mutual Compression of the Right Main Bronchus and an Abnormal Left Pulmonary Artery as Causes of the Death of a 7-Week-Old Child.

By

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In 1789 Bayford described an anomalous right subclavian artery which compressed the esophagus of an old woman with long standing dysphagia. Since then pathologists and roentgenologists have made numerous reports on anomalous large vessels compressing the esophagus or the respiratory tract. These anomalies can always be traced back to the original fetal vessels. They develop from vessels which in man normally recede, whilst those vessels which normally develop, regress and disappear. When occurring as isolated anomalies they rarely cause clinical signs and symptoms (25), as they usually do when combined with malformation of the heart. Isolated anomalies of the large thoraric arteries and veins are, therefore, usually casual discoveries on X-ray examination or at autopsy. Even where evident compression of the esophagus or the respiratory tract has been present, it seldom appears to cause any trouble (2, 8, 16). Though symptoms from the esophagus and the respiratory tract have been reported repeatedly (1, 7, 9, 10, 11, 13, 15, 22, 23), the number of such cases is small compared with the large number of cases without symptoms.

The great advance of recent years in thoracic blood vessel surgery (3, 4, 5, 11, 20, 24) has opened up new possibilities for the treatment of patients with serious complaints due to anomalies of the large thoracic vessels, and have thus given their signs and symptoms a new clinical importance. One may therefore be justified in reporting a case where an anomalous left pulmonary artery caused respiratory and circulatory disturbances which led to death.

Case History. J. nr. 11818/1947. G. H. R., male, born March 7, 1947. His parents were healthy and there were no hereditary malformations. The mother had a negative Wassermann reaction and had never

had rubella. Following a normal pregnancy, delivery in the maternity clinic of the Rikshospital was uncomplicated. The child was fullgrown, with normal weight and length. It was cyanotic, but cried immediately after birth. In spite of analeptics and aspiration from the respiratory tract, the cyanosis persisted and breathing remained rapid. The day after birth respiratory sounds over the left half of the chest were louder than normal, whilst they were almost inaudible over the right half. The following day X-ray examination revealed atelectasis of the right upper and middle lobe and emphysema of the lower lobe. The left lung and the heart showed nothing abnormal. During the following days there were repeated attacks of cyanosis and rapid respiration. At one week after birth the breathing sounds over the right lung were normal or slightly bronchial and over the left lung normal. The heart-sounds were also normal. From the 9th day there were no attacks, and from the 12th day lung conditions were normal on auscultation and on X-ray examination. As the child continued to be free from attacks, its general condition remained good, and its weight increased, it was discharged from the maternity clinic when 2 weeks old.

Two weeks later, however, the boy again had an attack like the previous ones, this time lasting for 24 hours. After this he had several attacks but none was serious until he was 6 weeks of age.

His attacks of dyspnea and cyanosis usually occurred in connection with meals. When the attacks began he often emitted a short cry, stretched out his body, and bent backwards. There was no stridor.

When six weeks old the boy caught a slight cold and again developed pronounced dyspnea and cyanosis. After repeated attacks during the course of three days, with cyanosis persisting even during the intervals, his condition deteriorated rapidly and he was admitted to the Ear, Nose and Throat Dep't of the Rikshospital on April 29, 1947.

On admission the boy had an attack. There was some retraction of the epigastrium, but no stridor, and his voice was clear. Dyspnea and cyanosis were pronounced, and, as noted during previous attacks, he had no fever. X-ray examination (which on account of the boy's restlessness was unsatisfactory) disclosed a displacement of the heart to the left, and probable emphysema of the right lung but no lung infiltration. Ordinary clinical examination revealed nothing further of importance to the diagnosis. Repeated attacks aggravated his condition, and the child died twelve hours after admission.

The attacks of cyanosis and dyspnea, without stridor, their connection with meals, the varying results of lung examination, the normal heart-sounds, all pointed to the possibility of a vascular anomaly interfering with the trachea or a main bronchus.

The autopsy performed the following morning by Dr. G. Thorsrud at the Institute of Pathology of the Rikshospital disclosed an isolated anom-

ly of the left pulmonary artery. Dr. Thorsrud has kindly submitted for publication the following report and figures.

»The normal left pulmonary artery is completely missing. The obliterated ductus arteriosus branches directly from the truncus pulmonalis and leads in the normal way to the aortic arch. The truncus pulmonalis continues as a normally situated right pulmonary artery which in the right hilus divides into the usual branches to the right lung. Immediately medial to the first artery to the right lung, however, a large vessel branches from the upper side of the right pulmonary artery, crosses over the right main bronchus, turns to the left, and passes behind the bifurcation and the left main bronchus to the left lung hilus. Here it branches in the usual way. Apart from this abnormal left pulmonary artery no anomalous vessel has been discovered, and on gross examination the heart is normal. The right lung is in part emphysematous, and in the left lung edema and widespread atelectasis is noted. Microscopically the anomalous left pulmonary artery is like a normal pulmonary artery. The left lung shows atelectasis, interstitial edema, and a slight bronchitis. The liver is microscopically normal.«

The tautness of the loop of the left pulmonary artery entangling the right main bronchus makes it reasonable to presume that this anomalous artery compressed the right main bronchus and its first branches, simultaneously becoming compressed itself. Thus may be explained the atelectasis of the upper and middle lung lobe present two days after birth, caused by complete compression of their supplying bronchi. The subsequent emphysema of the entire right lung may be explained in the same way, as a checkvalve mechanism produced by incomplete compression of the right main bronchus. The intermittent character of the patient's symptoms may have been caused by the movements and length and volume changes of the tracheobronchial tree during respiration. Judging from observations in adults (18), one would expect deep inspiration of diaphragmatic type to reduce the pressure exerted by the left pulmonary artery on the right main bronchus, whereas, conversely, expiration would increase it. In this way there may be a causal connection between the occurrence of the attacks during meals and the boy's spontaneous reaction of stretching his body and leaning backwards, thus making his diaphragm descend. The slight bronchitis in the course of a cold was then sufficient to convert the previously intermittent bronchial obstruction into a permanent check-valve obstruction causing emphysema of the right lung with subsequent displacement of the mediastinum.

Neither the atelectasis of the right lung's two upper lobes, nor the emphysema of the entire right lung should alone have been able to produce the pronounced cyanosis and dyspnea during the attacks. Interruption of the blood supply to the left lung through compression of the anomalous left pulmonary artery where it crossed the right main bronchus must have

Fig. 1.

been a contributory and probably the major cause of the patient's symptoms. The gross and microscopical examination of the left lung may support this view.

Normally the fetal pulmonic artery on each side branches from the sixth aortic arch. Congenital absence of one lung artery most often occurs on the left side (14), but it has also been recorded on the right (7). Where a normal lung artery is missing the possibilities of a vicarious blood supply to the lung are numerous. Comprehensive reports on these possibilities will be found in the literature concerning congenital pulmonic stenosis and pulmonic atresia. By means of the numerous anastomoses existing between the pulmonic and the systemic vessels in the distant parts of the lung lobes, bronchial or anastomosing esophageal and pleuro-pericardial arteries may act as a pulmonic artery where this is missing (25). The same holds true for the veins (10, 15, 19, 21). Doehle and Glaevecke (9) in 1897, and Scheid (22) in 1938 reported a case where the clinical and

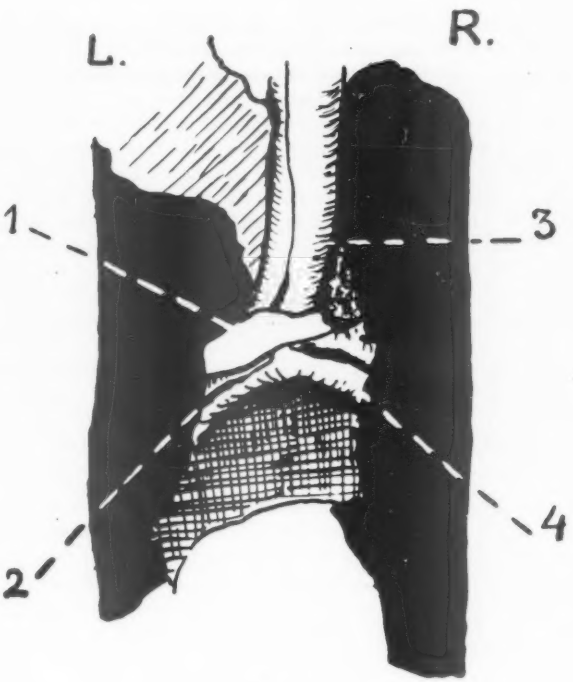

Fig. 2.

Fig. 1 and 2. Photogram and semi-diagrammatic drawing given the dorsal aspect of the preparation. The thoracic aorta displaced upwards and to the left. The anomalous left pulmonic artery (1) entangling the root of the right main bronchus (4) and compressing it. The unaffected left main bronchus (2) continuing in the direction of the lower trachea (3), which is displaced to the left.

autopsy findings were substantially the same as those reported here. Scheid assumes the anomaly to be the result of »ein Missverhältniss der Lagebeziehung zwischen Pulmonalanlage einerseits, Kiemenbogenarterien und primären Lungenarterien andererseits». He thus suggests that the anomalous lung artery is developed from a normal fetal lung artery. It is difficult to see how this suggested displacement of the fetal lung artery in relation to the lung bud might occur. When the fetal lung bud, at about the 4—5 mm stage, begins to separate from the foregut, the sixth pair of arch arteries appear on a level with the cranial part of

the lung bud (12, 17). Here an artery plexus develops around the foregut and the lung bud. Whilst the embryo grows from 5 mm to 8 mm in length, the separation of the two primordials takes place by formation of a groove on either side. These grooves deepen and first unite caudally. The separation of the lung bud from the foregut then proceeds in a cranial direction, and when incomplete may result in the formation of congenital fistulas between the esophagus and the trachea or a main bronchus. It is, therefore, difficult to imagine how the left sixth aortic arch, or its descending pulmonic artery, could appear to the right of the trachea. In Scheid's case, as in the present one, the ductus arteriosus was normal. As this duct is the remnant of the left sixth aortic arch artery, there is little probability of a displacement of the kind suggested by Scheid. It would appear to be more reasonable to assume that a normal primary left lung artery has not developed at all, and that the reported anomalous left pulmonary artery is due to a further development of collateral vessels of the fetal mediastinal artery plexus connecting the two lung hili. The anomalous left pulmonary artery is therefore to be regarded in the same way as the abnormally developed systemic arteries supplying the lungs in cases of congenital pulmonic stenosis and pulmonic atresia.

Conclusions. The anomalous lung artery described must be assumed to be the result of the development of collateral vessels connecting the two lung hili in the fetal mediastinal artery plexus. The patient's symptoms, dyspnea and cyanosis, are due to a mutual compression of the anomalous left pulmonary artery and the right main bronchus. A clinical condition in infancy revealing attacks of dyspnea and cyanosis, without stridor and without fever, especially in connection with feeding may be due to interference of anomalous vessel with the trachea or bronchi. Recent surgical progress has made some intrathoracic vascular anomalies the object of effective treatment and thus rendered the diagnosis of such conditions more significant.

Summary.

The case history of a 7-week-old boy. From birth the child had repeated attacks of cyanosis and dyspnea, without stridor. Lung examination two days after birth disclosed atelectasis of the upper and middle lobe of the right lung, and later emphysema of the entire right lung was found. At the age of 7 weeks a cold aggravated the infant's condition, and death followed repeated attacks over a three-day period. Autopsy revealed an abnormal left pulmonary artery to be the cause of the symptoms. Branching from the right pulmonary artery the anomalous left pulmonary artery entangled the right main bronchus and compressed it. The mechanism of the intermittent mutual compression of the anomalous artery and the right main bronchus is discussed. The author discusses the

nature of the anomalous left pulmonary artery and believes it to have been similar to that of the anomalous arteries supplying the lungs in cases of congenital pulmonic stenosis and pulmonic atresia.

Résumé.

L'histoire morbide d'un enfant âgé de 7 semaines est donnée. Dès la naissance l'enfant a eu des attaques de cyanose et de dyspnée, sans aucun stridor. L'examen des poumons à l'âge de deux jours, a decouvert atélectatique le lobe supérieur et le lobe moyen du poumon droit, et plus tard le poumon droit est trouvé entièrement emphysémateux, à l'âge de sept semaines un rhume a aggravé son état, et l'enfant est mort en suite des attaques répétées pendant trois jours. L'autopsie a demontré une artère pulmonaire gauche abnorme, qui, partissant de l'artère pulmonaire droite, fait le tour du bronche principal droit et le comprime. La méchanisme de la compression reciproque intermittente de l'artère pulmonaire gauche abnorme, et le bronche principal droit, est discutée. L'auteur en suite discute la nature de cette artère abnorme, et arrive à l'avis qu'elle soit la mème que celle des artères abnormes fournissant les poumons en cas de sténose et d'atrésie pulmonaire congénitale.

Zusammenfassung.

Krankengeschichte eines sieben Wochen alten Kindes. Von der Geburt hatte das Kind wiederholt Anfälle von Cyanose und Dyspnoe, ohne Stridor. Bei der Lungenuntersuchung wurde zwei Tage nach der Geburt Atelektase des oberen und mittleren rechten Lungenlappens nachgewiesen, und später ein Emphysem der ganzen rechten Lungen. Eine Erkältung verschlimmerte die Zustand des Kindes, dass, im Alter von sieben Wochen, nach wiederholten Anfällen im Laufe von drei Tagen, starb. Die Obduktion ergab eine abnorme linke Lungenarterie als Ursache der Symptome. Von der rechten Lungenarterien abzweigend umschlingt die abnorme linke Lungenarterie den rechten Hauptbronchus und drückt ihn zusammen. Die Mechanismus der gegenseitigen Compression der abnormen linken Lungenarterien und des rechten Hauptbronchus wird auseinandergesetzt. Verfasser diskutiert die Natur der abnormen Lungenarterien, und nimmt an dass sie dieselbe sei als die der abnormen Arterien die bei angeborenen Pulmonalstenose und Pulmonalatresie die Lungen Blut zuführen.

Resumen.

Se relata la historia mórbida de un niño de 7 semanas de edad. Desde el nacimiento tuvo ataques de cianosis y de dispnea, sin estridor. El examen de los pulmones, a los 2 días de edad, descubrió atelectasia del lóbulo superior y del lóbulo intermedio del pulmón derecho, encontrándose

más tarde que este último estaba enteramente enfisetamoso. A la edad de 7 semanas un catarro agravó su estado y el niño falleció a causa de ataques repetidos durante 3 días. La autopsia demostró una arteria pulmonar a la izquierda, la cual era anormal. Esta arteria, que salía de la arteria pulmonar derecha, daba la vuelta alrededor del bronquio principal derecho y lo comprimía. El mecanismo de compresión recíproca e intermitente de la arteria pulmonar izquierda anormal, y el bronquio principal derecho se discute. El autor discute la naturaleza de esta arteria anormal y llega a la conclusión de que es la misma que la de las arterias anormales que abastecen los pulmones en caso de estenosis y de atresia pulmonar congénita.

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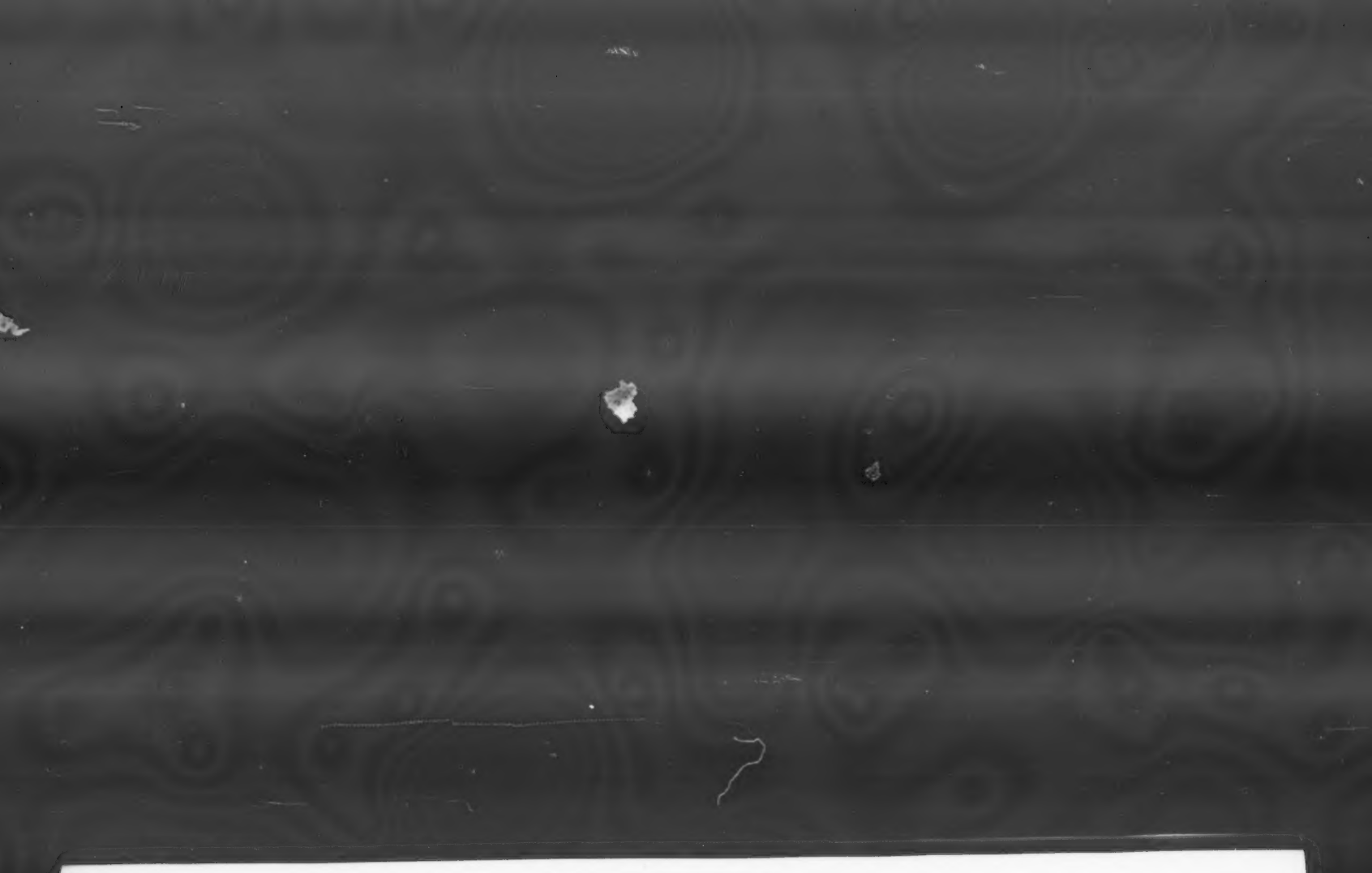

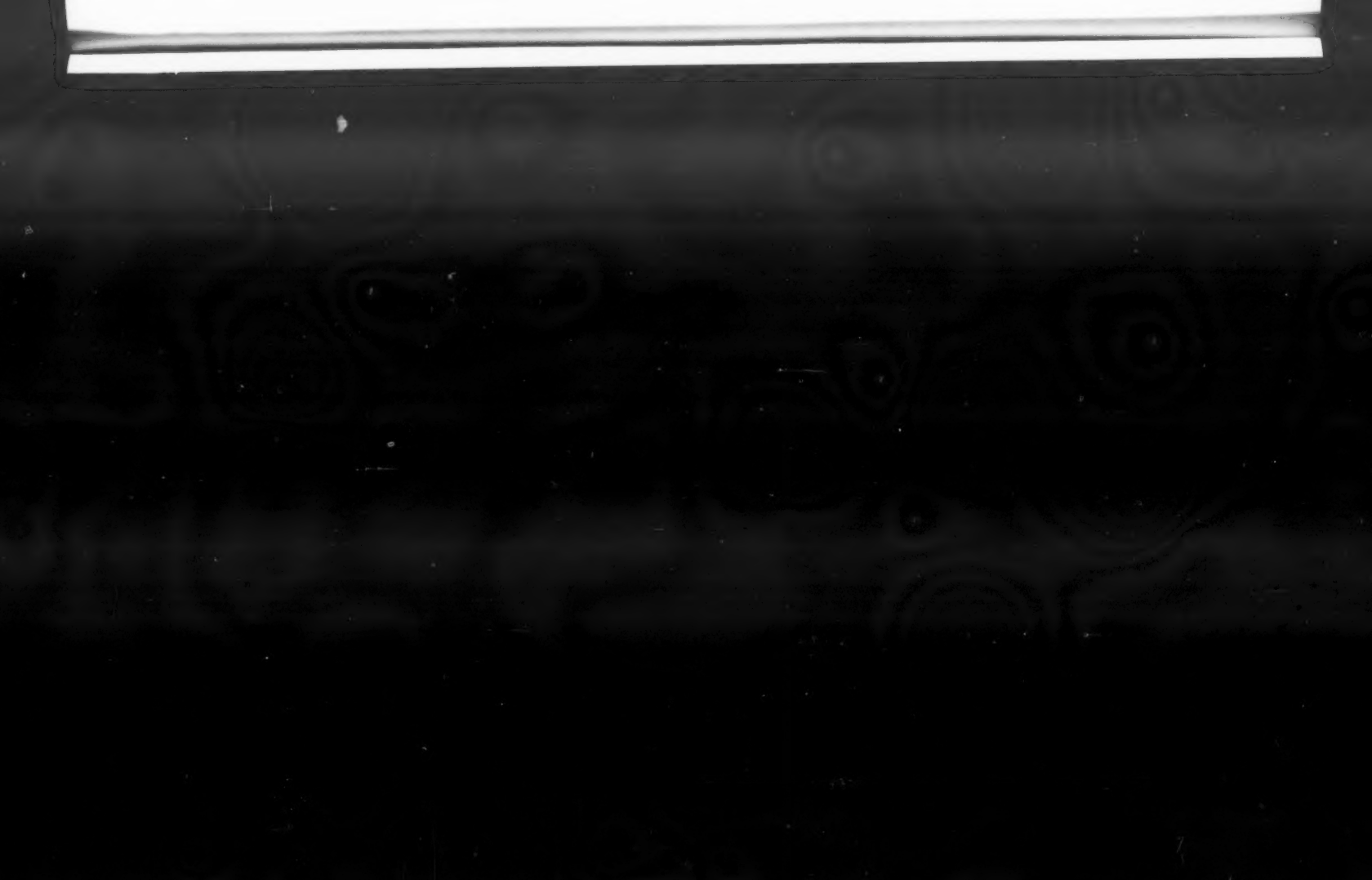

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(FROM THE QUEEN LOUISE HOSPITAL FOR CHILDREN, COPENHAGEN.
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Niemann-Pick's Disease

Acute and Chronic Type?

By

AAGE VIDEBÆK

In 1914 NIEMANN (51) described a new syndrome closely resembling Gaucher's disease, but differing from the latter in exhibiting diffuse changes in all organs. Similar descriptions followed in rapid succession. SIEGMUND (62) found ample lipoid in the spleen and liver, but it was PICK (54) who emphasized the characteristic features of the disease and defined it clearly. BLOOM (10) demonstrated hyperlipemia and DIENST (19) an increased storage of phosphatides in the organs, whereas KLENK (7) found that it was not only a question of lecithin as demonstrated by HAMBURGER (30), but particularly of a storage of sphingomyelin encountered not only in the reticulo-endothelial cells, but also in the cells of the parenchymatous organs. Later intravenous injection of lecithin emulsion was found to produce the characteristic changes in the experimental animal (9, 25).

The writer has had the opportunity to observe a patient who was affected with the disease for more than 3 years until at the age of $5\,^1/_2$ years death at last took place.

Case Report

There are no Jews in the family, which is known for 4 generations and is healthy without any known cases of splenohepatomegaly on either side. The paternal grandmother died of breast cancer and the maternal grandmother is suffering from a benign diabetes mellitus. The father was 31 and the mother 28

years of age when the patient was born. Two siblings are healthy. There are no cases of consanguinity in the family.

The patient was born at term after a labor of 36 hours. Birth weight 3 700 g. The boy grew up in the country under satisfactory

Fig. 1. Boy of 26 months with Niemann-Pick's disease.

hygienic and social conditions. In spite of breast-feeding for 6 months and administration of vitamins D and C, the first tooth did not appear until the age of 13 months. He was 10 months old before he could sit up and 20 months before he could walk. At the age of 1 year he had bilateral otitis media and at 2 whooping cough complicated by bronchopneumonia.

The child was hospitalized at the age of 26 months. He was dystrophic (Fig. 1), with very sparse subcutaneous tissue, slack muscles, and a large abdomen. There was marked pigmentation

of the elbows and the dorsal aspect of hands and feet, particularly the knuckles and terminal phalanges, but no pigmentation of the mucous membrane of the mouth. Lymph nodes were palpable everywhere, their size being up to that of a hazel nut. There was

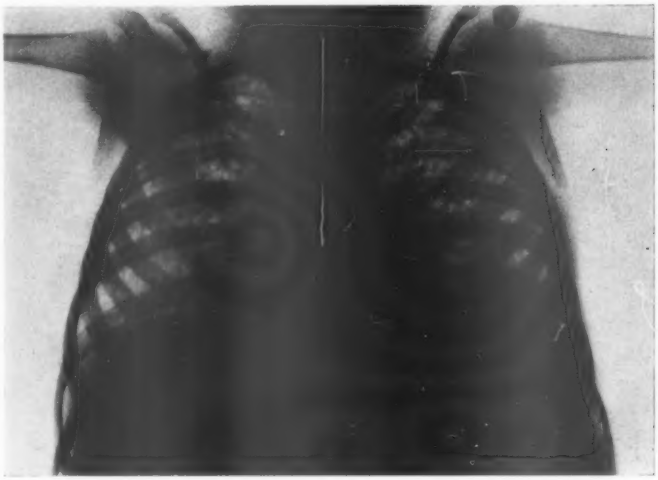

Fig. 2. Diffuse pulmonary changes in the boy at the age of 2 years.

enormous enlargement of the spleen and especially the liver and slight ascites but no edemas.

X-ray of the skull and long bones revealed diffuse halisteresis and delayed bone development. X-ray of the lungs (Fig. 2) showed a diffuse, speckled, lacy pattern in both lung fields, but stethoscopy was normal. Ophthalmoscopy showed the fovea centralis and the optic disc to be normal. There were no neurological symptoms.

Tuberculin test negative, blood Wassermann negative. Urine contained no sugar, urobilin, albumin, acetic acid, or acetone. Erythrocyte sedimentation rate 3—12 mm, Hb. about 90 per cent, color index 1.00, reticulocytes 1.2 per cent, the fragility of the red corpuscles normal, icterus index 7—14. Leukocytes about 10 000, lymphocytes about 70 per cent, monocytes about 3 per cent,

polynuclears about 25 per cent, a few plasma cells. A few of the mononuclear cells had an ample cytoplasm with monstrous vacuolization. Bone marrow punctate from the tibia showed a slightly reduced erythropoiesis, a normal myelopoiesis, and one enormous

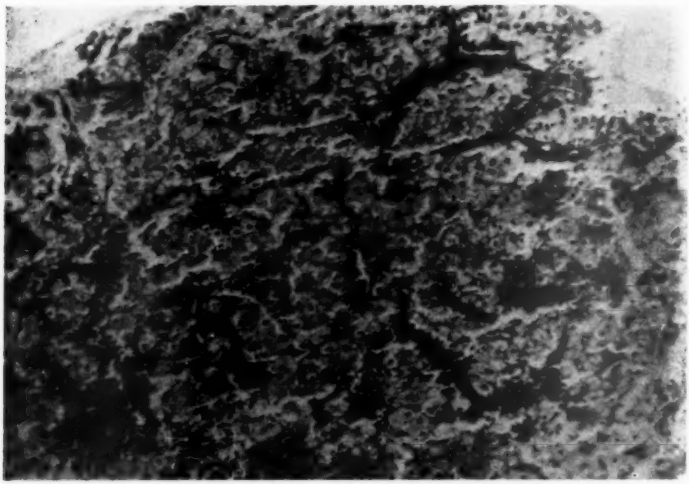

Fig. 3. Biopsy from the spleen in which numerous foam cells predominate.

foam cell. Thrombocytes 122 000, prothrombin time slightly prolonged, bleeding time 4 minutes, clotting time normal. Fasting blood sugar 70—80 mg per cent, glucose tolerance test showed a rather flattened and prolonged curve. Serum calcium 10.1—10.0 mg per cent, blood phosphorus 4.1—4.1 mg per cent, serum phosphatase 227—150 (normal values), serum albumin 4.9—5.0 per cent, serum globulin 2.0—1.7 per cent, total fat 925 mg per cent, phosphatide 173 mg per cent, total cholesterol 290 mg per cent, free cholesterol 101 mg per cent.

Aspiration biopsy from the spleen showed strands of large cells holding lipoid (Fig. 3). In the smear of the punctate from the spleen there were several cells of the same appearance as those from the tibia marrow punctate (Fig. 4), being up to 80 μ with 1 to 2 nuclei. Biopsy from the liver revealed a similar picture. The

hepatic cells were filled with glycogen and vacuoles with numerous lipoid droplets which did not stain with osmic acid, but those from the peripheral areas of the cells stained red readily with Sudan III and blue-black with Smith-Dietrich stain.

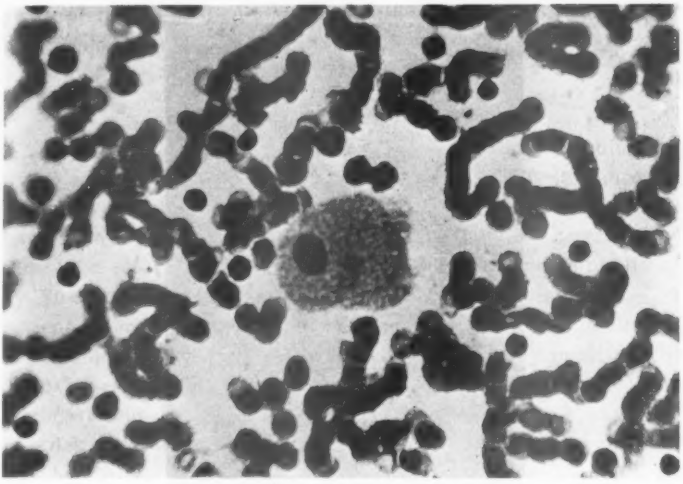

Fig. 4. Smear from the splenic punctate showing a foam cell.

Treatment with insulin and liver extracts resulted in marked improvement, and the patient was discharged.

Aged 3 $^1/_2$ years: Longitudinal growth only 1 $^1/_2$ cm against 7 cm normally, increase in weight only 1 $^1/_2$ kg against 2 kg normally. The brownish pigmentation was more marked and the enlargement of the spleen greater (Fig. 5) while that of the liver remained unchanged. Ophthalmoscopy revealed normal discs, but now the fovea centralis was red and surrounded by a grey zone suggestive of the appearance in Tay-Sachs' amaurotic idiocy. No neurological symptoms; occasionally epistaxis. Hb. 79 per cent, color index 0.96, leukocytes 12 300, lymphocytes 46 per cent, polynuclears 49 per cent. Serum calcium 9.8 mg per cent, blood phosphorus 13 mg per cent. Total cholesterol 225 mg per cent,

free cholesterol 86 mg per cent, serum albumin 5.1 per cent, serum globulin 2.1 per cent.

Aged 4 years: Felt better than the year before. Weight 14 $^{1}/_{2}$ kg, less dyspnea, occasionally epistaxis. Lipoid was not demonstrable in the urine upon chemical analysis.

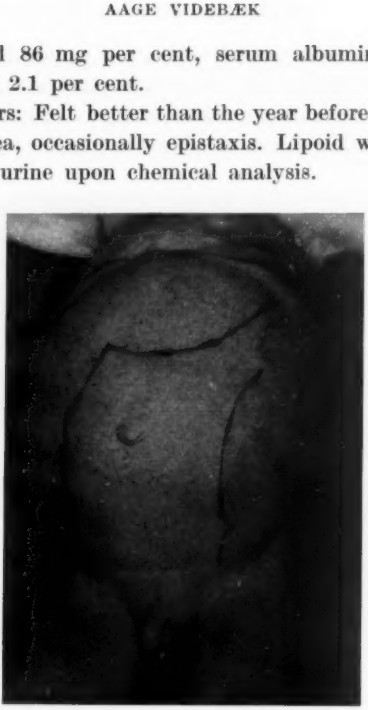

Fig. 5. Size of the spleen and liver in the same case at the age of 3 $^{1}/_{2}$ years.

Aged 5 $^{5}/_{12}$ years: the boy was still receiving insulin and liver extracts as well as vitamin K, but the least elevation of temperature was attended with extensive petechiae. The enlargement of the spleen was more pronounced, as was the ascites. The boy died in the home after having developed bilateral pneumonia and simultaneous violent diarrhea. Autopsy was not allowed.

Summary of the Case: A boy who had been ailing ever since birth exhibited splenohepatomegaly, universal enlargement of the lymph nodes, pigmentations, and x-ray evidence of diffuse halisteresis and extensive pulmonary changes. Tibia marrow punctate and spleen punctate revealed foam cells and biopsy

specimens from the spleen and liver large cells holding lipoid and staining with Sudan III. Hyperlipemia. Improvement after treatment with insulin, liver extracts, and vitamin K. At the age of $3\,^1/_2$ years the patient exhibited a red fovea centralis and an increased content of phosphorus in the blood. After more than 3 years of illness he died at the age of $5\,^1/_2$ years. There was enormous enlargement of spleen and liver.

Incidence and Prevalence

A total of 73 cases of Niemann-Pick's disease, including the writer's, have been reported in the literature. At first glance the number appears to be larger, but that is because some of the cases have been reported more than once. Thus one case described by CORCAN *et alii* (17) has also been taken to be a new one published by NORDMANN (52) who, therefore, has only one original case. A patient described by DIENST & HAMPERL has later been dealt with in more detail by DIENST (19). A patient originally published by SOBOTKA *et alii* (64) was again described by GOLDSTEIN & WEXLER (28) and by WASCOWITZ (70). FREUDENBERG'S case (27) was described again by LOEBELL (45).

The disease is equally common in both sexes (34 boys, 35 girls, 3 of unknown sex) but occurs with striking frequency among Jews (29 Jews, 26 Non-Jews, 18 of unknown race). Among the Jewish patients the girls predominate (9 boys, 18 girls, 2 of unknown sex), whereas the sex ratio among Non-Jews is 15 boys: 11 girls. Its occurrence has been described as often in Europe as in the U. S. A., one case has been reported from Turkey (23), one from Japan (67), and one from Australia (2, 69), but Niemann-Pick's disease has not so far been observed among Negroes.

Etiology and Pathogenesis

Familial occurrence has been found with certainty in no less than 9 cases 27, 38, 41, 46, 53, 71, (17, 52), (42, 48), (19, 65), always among siblings, 8 times among 2 siblings and once among 3 siblings. In 3 additional cases familial occurrence is likely, a brother or sister having died in childhood with enlargement of

the spleen and liver. Accordingly, familial occurrence has been reported in nearly 30 per cent of the cases. Nevertheless the disease has not yet been demonstrated in more than one generation, presumably because it has been known only for a short time.

In a brother and in a cousin of a patient with Niemann-Pick's disease v. BOGAERT (11) found Tay-Sachs' amaurotic idiocy, from which two other members of the family were probably also suffering. This observation is of immense interest on account of the great resemblance between the two diseases. Another family study (53), at least as interesting, has revealed in addition to familial occurrence of Niemann-Pick's disease several members of the family with either splenohepatomegaly, hyperlipemia, hypercholesterolemia, or an increased amount of phosphatase in the blood. This study is absolutely worth repeating, although a thorough family study may give a negative result (7).

Now and then Niemann-Pick's disease has been found to coexist with developmental abnormalities (spina bifida (39), hypospadia (20), defects of the fingers (10), abnormal hairing (35), hydrocephalus (57)), and several patients have exhibited the so-called mongolian spots (8, 33, 42, 48, 59, 60). Consanguinity has been reported in 3 cases (36, 64, 68).

A large number of factors thus indicate the significance of heredity. To them may be added the age distribution.

Fig. 6 gives the age distribution at death, as this is the approximate time at which the disease has been diagnosed in a large number of the cases. Thirty three per cent died during the first year of life and 43 per cent during the second year, whereas only a few of the patients lived to be older than 2 years. Two patients reached the age of $5\,^1/_2$ years, and the condition has been observed in 2 brothers (53) who died at the ages of 29 and 33 years, respectively. No doubt the vastly predominant group in early childhood has its particular pathogenesis, in which hereditary factors presumably play an essential rôle. In numerous cases enlargement of the spleen or liver has been observed shortly after birth, while in other cases the disease has been diagnosed later, but in the latter the symptoms have been so marked that the disease was no doubt present for some time. It may be congenital in all cases; at least

the mental as well as the somatic development of the children is retarded.

Co-existing diseases (otitic meningitis (10), pulmonary tuberculosis (71), primary carcinoma of the liver (72), hydrocephalus (57)) do not give any indication as to the pathogenesis.

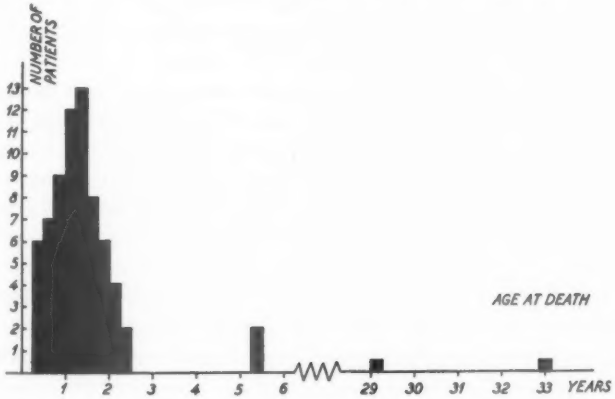

Fig. 6. Age at death in 73 cases of Niemann-Pick's disease.

A thorough discussion (7, 21, 54, 66) of the pathogenesis goes to show its obscurity and our limited knowledge of the most elementary processes going on in normal and diseased cells. The characteristic feature of Niemann-Pick's disease is an immense intracellular lipoid accumulation, particularly of sphingomyelin, much less of cholesterol and neutral fat, but not necessarily attended with changes in the lipoid content of the blood, even though the amount of total fat or cholesterol in the serum may be enhanced. Lipoid analyses of the spleen and liver have been made in 17 cases. A large number of investigations, int. al. by THANNHAUSER (66), indicate the likelihood of the following pathogenesis: The ceramide lignoceryl sphingosine is met with in a normal liver and spleen. By esterification with choline phosphoric acid sphingomyelin is formed by a process which is reversible and the course of which depends on the cerebrosidase and phosphatase. The increased concentration of sphingomyelin may be due either

to an increased synthesis (increased phosphatase activity) or to a decreased splitting of phosphoric acid, but at any rate to the course of the reversible process being in favor of the formation of sphingomyelin.

Lignoceryl-sphingosine + choline phosphoric acid ⇄ sphingomyelin.

Clinical Features

The vast majority of the patients are infants who in many cases have been ailing right from birth. They are small and slender, dentition is delayed, they stand and walk late, and at times the development of the ossification centers is delayed, but there are no signs of rickets. There will usually be dyspepsia, and gradually emaciation becomes extreme, the appearance being athreptic, but with a very large abdomen on account of the enormous enlargement of the liver and spleen. In some cases a mongoloid appearance with protrusion of the tongue has been reported (1, 7, 14, 26, 31, 34, 51). This is interpreted as the cause of bulbar paralysis (7). In addition, the children are often mentally retarded or idiots (5, 7, 18, 40). A few exhibit exophthalmos (8, 24, 30, 49, 59, 63). In 1/3 of the cases there is marked pigmentation of the skin, particularly on the extensor surfaces of the joints, rarely involving the mucous membrane of the mouth (4, 66), or in the form of mongolian spots, or else the skin is reported to be brownish-yellow. Often there will be a speckled or papular rash in the face and on the neck (10, 46, 68). Petechiae may occur.

Rigidity and hyperreflexia is encountered in about 1/5 of the patients, nystagmus in about 1/8. Ophthalmoscopy has been performed in only 33 cases. Twenty of them (60 per cent) showed — at times at a late stage of the disease — a red fovea centralis surrounded by a greyish zone; the fovea is often reddish brown, brown, seldom black (36). The optic disc may at the same time be either normal or totally or partially pale, resulting in amaurosis. RINTELEN (58) gives a detailed description of the ophthalmoscopic appearance, which he finds different from that in Tay Sachs' disease.

Ear deafness is sometimes noted (20, 45).

Half the patients are reported to have had a moderate generalized lymph node enlargement.

Cough and expectoration with febrile periods are ordinary findings, but râles are rare. The x-ray film of the lungs will show either hilar infiltration (1, 53, 56) or diffuse changes as in miliary tuberculosis (7, 10, 27, 36, 65).

The large distended abdomen often gives the first hint of actual disease. The margin of the enlarged spleen and liver is sometimes visible through the thin abdominal wall.

X-ray examination of the skeletal system usually shows marked halisteresis and focal osteoporosis in the long bones. Spontaneous fracture may occur (27). X-ray of the abdomen may show diffuse calcification of the adrenal glands (2).

Examination of the blood usually reveals moderate hypochromic anemia which, however, may be severe, even down to 20 per cent (3). In about 1/3 of the cases there is moderate leukocytosis, but this too may be pronounced — up to 88 000 (19). Strangely enough leukopenia is never met with. In 1/4 of the cases there are large vacuoles in the cytoplasm of the mononuclear cells. There may be occasional erythroblasts, plasma cells and reticulum cells in the blood. Thrombopenia has been reported (46, 64, 71), but as a rule the platelet level is normal, as are also bleeding time and clotting time. Hemorrhagic diathesis with development of cutaneous hemorrhages is rare (3, 24, 29), two patients died from intestinal hemorrhage (15, 22).

The serum lipoid level is sometimes enhanced, the highest values found being 1 610 mg per cent (36) and 1 430 mg per cent (64). The serum total cholesterol is only occasionally enhanced (16, 30, 46), but free cholesterol makes up from 35—94 per cent of the total cholesterol in the serum; the phosphorus lipoid level, on the other hand, is not enhanced. Serum phosphorus may be high and serum phosphatase perhaps high, but it is difficult to estimate the values reported. Fasting blood sugar is low or normal.

Often the bone marrow punctate contains the typical foam cells (61) and at times numerous reticulum cells or monocytes (36, 49).

The urine sometimes contains lipoid. The spinal fluid is normal, apart from a positive Pandy test.

Pathology

Autopsy has been performed in 2/3 of the cases and the pathological changes are therefore well known. There are Niemann-Pick cells in every organ and every tissue. The lipoid accumulates in droplets in the cytoplasm in the reticulo-endothelial system, endothelium, connective tissue (not in skin and muscular tissue), and the parenchymatous cells of all the organs, enlarging these cells and changing their normal appearance. The lipoid did not reduce osmic acid, but stain from light red to brownish with Sudan III and blue with Nile blue sulphate and with Smith-Dietrich stain after having been prepared with potassium permanganate.

The weight of the spleen in 30 infants is known. It ranged from 30 g (57) to 1 120 g (3), averaging 230 g. The liver too was enlarged, weighing between 140 g (14) and 1 750 g (61) (averaging 615 g); the cut surface is greasy. The enlargement of the lymph nodes, which was usually moderate, was most common and most pronounced in the mesentery. The adrenal glands are sometimes stated to be enlarged (17, 32, 39, 46, 61) or calcified (2).

Detailed descriptions (7, 34, 43) have been given of the peculiar changes in the central nervous system, which are diffuse but most marked in the cerebellum.

Attempts at *treatment* have so far been in vain. Splenectomy has been performed in 12 infants, 5 of whom died shortly after and 5 in connection with the operation; 2 of the children survived 2 and 6 months after the splenectomy (3, 10). It is not, however, only for technical reasons that operation is not advisable, but also because of the spread of the disease in other organs. X-ray therapy appears to be ineffective (33, 71) as does radium applied to the spleen (11, 38). A diet poor in fats has been tried without success (30). Improvement has been seen following administration of liver extract (12). The writer's patient was treated with liver extract, insulin, and vitamin K. Perhaps this treatment was the cause of the unusually protracted course. The boy's general condition improved shortly after the institution of the treatment; his appetite became better, he gained weight, and the enlargement of the spleen temporarily subsided.

Course and Prognosis

As the abdomen goes on growing and the dystrophy is exacerbated, the disease runs a fatal course, often after a complicating pneumonia or increasing neurological symptoms (ophistotonus or

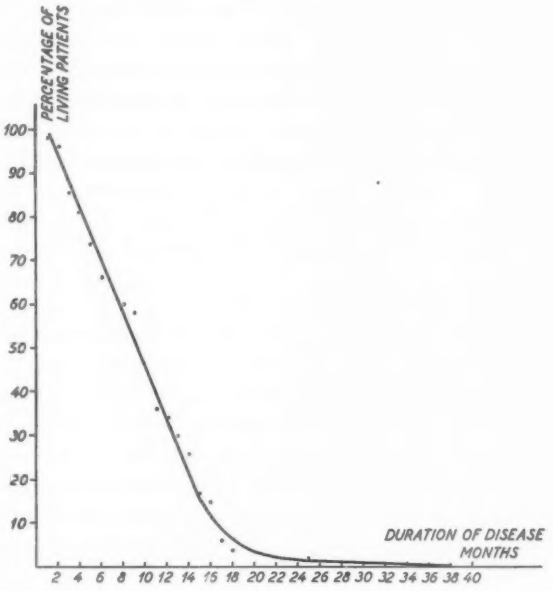

Fig. 7. Survival diagram based on the estimated duration of the disease in 47 cases of Niemann-Pick's disease.

complete idiocy). Ten patients died in connection with splenectomy, 2 from intestinal hemorrhage, and a few from sepsis. It is difficult to evaluate the duration of the disease, as it is usually diagnosed at an advanced stage. The time elapsing from the finding of an enlarged spleen and liver until death is known in 47 cases, in which it averaged 9 months. The survival diagram (Fig. 7) shows that 50 per cent of the children died after about 9 months' illness, 75 per cent died after more than 1 year's illness, and only

2 survived 1 1/2 years after the disease had been diagnosed. The case reported in this paper has run the longest course known so far or at least 38 months.

Diagnostic Criteria

Marked splenohepatomegaly, moderate generalized lymph node enlargement, brownish pigmentation of the skin, and a retarded somatic and mental development appear to have been reported in all cases. If the blood count also shows vacuolized leukocytes and ophthalmoscopy reveals a red fovea centralis, there is no doubt about the diagnosis. In the absence of the latter findings, the demonstration of foam cells, staining in the characteristic manner described above, is decisive. They are demonstrable in biopsy specimens from the spleen, liver, lymph nodes, and often in the bone marrow punctate. They may also be found in large numbers in the sputum (34).

Differential diagnosis is only from other conditions involving splenohepatomegaly. It is important to bear in mind that Niemann-Pick's disease does not occur exclusively in infancy, but it may also be found in older children and in adults and thus may be difficult to differentiate from Gaucher's disease. In such instances much help can be derived from ophthalmoscopy, lipoid staining of the foam cells, or lipoid analysis of biopsy specimens (23).

Summary

A case is reported of Niemann-Pick's disease diagnosed in a Danish boy, aged 26 months. Treatment with liver extract, insulin, and vitamin K resulted in temporary improvement. The disease ran a course of at least more than 3 years, a period far exceeding any observed hitherto, the boy living until the age of 5 1/2 years. On the basis of 72 cases from the literature and his own, set out in tabular form, the writer reviews the possible etiology, the pathogenesis, symptomatology, course, prognosis, and treatment of the disease. Niemann-Pick's disease is equally common in boys and girls, occurring most frequently during the

first 2 years of life, but sometimes being observed in older children and adults. Nearly half the children affected are Jewish. Familial occurrence has been reported in about 30 per cent of the cases, so far only among siblings. Age distribution and survival time are presented in tabular form. The average duration of the disease is 9 months.

Résumé

Un cas de la maladie de Niemann-Pick diagnostiquée chez un garçon danois de 26 mois. Un traitement par extrait de foie, insuline et vitamines K a amené un mieux temporaire. La maladie a eu une durée minimale de plus de trois ans, durée bien supérieure à ce qui avait été observé jusqu'ici, le garcon a vécu jusqu'à l'âge de 5 ans 1/2. Sur la base de 72 cas, de la littérature et des siens propres, mis sous forme de tableau, l'auteur passe en revue l'étiologie possible, la pathogénie, la symptomatologie, le cours, le prognostique et le traitement de cette maladie. La maladie de Niemann-Pick est également commune chez les garçons et chez les filles, se déclarant le plus souvent durant les 2 premières années de la vie, mais constatée quelquefois, chez des enfants plus âgés ou chez des adultes. Presque la moitié des enfants sont juifs. L'hérédité familiale a été rapportée dans environ 30 % des cas. Jusqu'ici seulement parmi les frères et sœurs. La répartition des âges et la durée de la survie sont présentées sous forme de tableau. La durée moyenne de cette maladie est de 9 mois.

Zusammenfassung

Ein Fall von Niemann-Pick's Krankheit bei einem 26 Monate alten dänischen Knaben. Behandlung mit Leberextrakt, Insulin und Vitamin K hatten zeitweilig Verbesserung zur Folge. Die Krankheit hatte einen mehr als dreijährigen Verlauf, ein nach den bisherigen Beobachtungen äusserst seltener Zeitraum, und der Knabe erlebte ein Alter von 5 $^1/_2$ Jahren. Auf Grund seines Falles und 72 Fälle aus der Litteratur, in Tabellenform zusammengestellt, untersucht der Verfasser die mögliche Ätiologie, Pathogenese, Symptomatologie, Verlauf, Prognose und Behandlung der Krankheit. Sie ist gleich häufig bei Knaben und Mädchen,

Author	Year	Sex	Jewish or Not	Age at Onset mo.	Age at Death mo.	Size of Liver g	Size of Spleen g
Niemann	1914	♀	÷	2	17	large	
Knox et al.	1916	♀	+	9	15	415	86
» » »	»	♀	+	5	10	420	100
Siegmund	1921	♀	+	1	9	large	270
Fahr et al.	1923	♂	+		21	large	large
Bloom	1925	♀	+		16	large	large
»	»	♀	+	7	21	large	538
»	»	♂	+		7	normal	62
Henschen	1926	♂				230	73
Schiff	1926	♂		3	17	large	large
Corcan et al.	1927	♂	÷	7	10	425	72
Löwy	1927		+	3	28	large	large
Hamburger	1927	♀	+	1	14	980	198
Abt et al.	1928	♀	+	6	17		135
Berman	1928	♀	+	2	15	583	123
Hess	1928			6	15		
Kramer	1928	♀	+	4	14		480
Lederer	1928	♀	+		15		480
Chwalibogowski et al.	1929	♀	+	$3^1/_2$	$18^1/_2$		
Dienst	1929	♀		2	5	large	large
Schmitz et al.	1929	♂	÷		20	1 750	480
Baty	1930	♀	+	1	16	477	82
Hassin et al.	1930	♂	+	1	18	large	356
Jenny	1930	♀			7	large	large
Kilchherr	1930	♂	÷	6	12	large	80
Smetana	1930	♀	+	$3^1/_2$	20	large	220
Sobotka	1930	♀	+	6	14	500	180
Stransky	1930	♂	÷	$4^1/_2$	5	large	large
Schaferstein	1931	♂	+	1	12	large	large
Druss	1932	♀	+	10	13		
Fisher	1932	♀	+		$7^1/_2$	large	large
Knox et al.	1932	♂		20	26	large	large
Winter	1932	♀	÷	6	15		550
»	»	♀	÷	4	8	large	large
Nordmann	1933	♂	÷		12	large	large
Pounders	1933	♀	÷	6	11	large	large
Tow et al.	1933	♀	÷	6	9	400	185
v. Bogaert	1934	♀	+	6	17	large	large
Vickery	1934	♀			11	large	large

Leuko-cytes Maximum	Thrombo-cytes Minimum	Hbg. %	Autopsy or Not	Lipid Analysis of Organ	Serum-lipid mg %	Serum-chole-sterol mg %	Serum-phos-phate
			+	÷			
25.400			+				
22.600			+				
			+				
5.800		36	+				
36.000			+				
23.400		45					
29.200		65	+			210	
			+				
10.800	200 000		÷			310	
14.500	394 000	85	+	+			
			÷				
16.800		93	+	+		650	
15.700		55	÷				
13.200		50	÷	+	560	231	
			÷	+	560		24.0
12.600	192 000	62	+	+		231	
12.600	220 000		+				
			+	÷		429	
88.000		50	+	+		240	
3.000		62	+			270	
35.000			+				
13.200	190 000		+	÷	737	150	17.5
9.300			+				
6.930		81	+	+			
18.000	70 000	61	+	÷	1 430	290	
9.920		58	÷			135	
15.000	220 000		+				
			+				
20.000	150 000	55	÷	÷			
22.400		75	+				
4.000	150 000	35	+				
7.600	80 000		÷				
			÷				
4.600		39	÷				
			+				
17.400		60	÷			212	
12.800		65	+				

(Cont.)

Author	Year	Sex	Jewish or Not	Age at Onset mo.	Age at Death mo.	Size of Liver g	Size of Spleen g	Leuk cyt Maxim
Baumann et al.	1936	♂	÷	10	27			
Espinos et al.	1936	♀	÷		26		large	
Guccione	1936	♂	÷	8	18	large	large	
Angel et al.	1937	♀		5	22	large	1 20	19.6
Höra	1937	♂	÷		25		30	6.4
Tokugawa	1937	♂	÷	5	17	large	905	5.1
Chevrel et al.	1938	♂			5½ y.			
Freudenberg	1938	♂	÷	9	17			6.0
»	»	♂	÷	9	19			13.0
Lignac et al.	1938	♂	÷		6			
Wood	1938	♀		8	14	750	large	
Bussel et al.	1939	♂	+	3	14	large	large	14.0
Merksamer et al.	1939	♀	+	1½	4	239	48	
» » »	»	♂	+	4½	22			22.0
Armand-Delille et al.	1940	♂			18	large	large	15.0
Ley	1940	♂	+		12	660	large	
Badanow	1941	♀	+	8	18	large	large	
Karelitz	1941			5				35.0
Kugelmass	1941		+	5	12	large	large	22.0
»	»							
Maurer	1941	♀		6	21	760	large	23.0
»	»	♂	+	3	21	large	large	16.7
»	»	♂	÷	4½	7½	large	95	18.0
»	»	♀	÷	8	11½	639	200	11.5
Reeves et al.	1941	♂	+		9	525	30	10.2
v. Cube et al.	1943	♂			24			9.0
Canmann	1944	♀	÷	3½	3½	140	50	20.4
Facatselli	1944	♀	÷	4	14			7.0
Alexander	1946	♂		1	3			6.0
Menten et al.	1946	♂			10	965	240	
Murray et al.	1946	♂		4	7½		950	9.1
Pfändler	1946	♂			29 y.			
»	»	♂			33 y.		2 000	7.0
Videbæk	1948	♂	÷	24	65	large	large	10.0

Leuko-cytes Maximum	Thrombo-cytes Minimum	Hbg. %	Autopsy or Not	Lipid Analysis of Organ	Serum-lipid mg %	Serum-chole-sterol mg %	Serum-phos-phate
			+	+	701	191	
			÷				
			+				
19.600		20	÷	+			
6.400		44	+	+	400	108	
5.100		71	+				
				+			
6.000			+		909	262	
13.000			+		831	192	
			+	+			
		68	+				
14.000		55	+			75	
	140 000		+	÷		240	
22.000							
15.000		46					
			+				
35.000		74	+		1 610	240	
22.000							
23.000	56 000	75	+	÷		170	
16.700		70		÷		332	
18.000	140 000	70	+	÷		132	
11.500	310 000	76	+	÷		171	
10.200		70	+	÷		156	
9.000		65		+		160	24.1
20.400			+	+		132	
7.000		35	+	+		280	
6.000			+				
			+	+			
9.100		58	+			165	
			+	+			
7.000		108	+	+	712	105	
10.000	122 000	90	÷	÷	925	290	17.3

tritt meist in den ersten 2 Lebensjahren auf, wird aber zuweilen auch bei älteren Kindern und Erwachsenen beobachtet. Fast die Hälfte der Kinder sind jüdisch. Familiares Vorkommen unter Geschwistern wurde in ca 30 % der Fälle berichtet. Die Altersverteilung und die Überlebenszeit ist in Tabellenform dargestellt. Die durchschnittliche Dauer der Krankheit ist 9 Monate.

Resumen

Se informa sobre un caso de la enfermedad de Niemann-Pick observado en un niño danés de 26 meses. El tratamiento con extracto de hígado, insulina y vitaminas K dió como resultado un mejoramiento temporal. La enfermedad duró por lo menos durante más de 3 años, lo cual excede de lo hasta entonces observado. El niño vivió hasta la edad de cinco años y medio. Basándose en 72 casos sacados de la literatura médica y en éste, el autor estudia la posible etiología, patogénesis, sintomatología, curso, pronóstico y tratamiento de la enfermedad. La enfermedad de Niemann-Pick es tan común en niños como en niñas y màs frecuente durante los dos primeros años de vida, pero también se ha observado en niños de mayor edad y en adultos. Casi la mitad de los niños son judíos. La presencia de la enfermedad en la familia se ha notado en el 30 por ciento de los casos, hasta ahora sólo entre primogénitos. La distribución por edades y el tiempo de supervivencia se han expuesto en forma tabular. La duración promedia de la enfermedad es de 9 meses.

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FROM THE FUGLEBAKKEN CHILDREN'S HOSPITAL, COPENHAGEN.
(CHIEF PHYSICIAN: VALDEMAR POULSEN, M. D.)

Psychosomatic Pediatrics

By

SVEND HEINILD

Introduction

Relations between the emotions and pathophysiological changes in the organism have been recognized to exist from the very beginning of the history of mankind and have been subjected to literary treatment at least as far back as Plato and Galen. And from the awakening of natural science proper, mention may be made of, among others, »Les passions de l'ame» (1649) by Descartes, who points out »that nothing affects the soul more than the body to which it is united».

The last century has contributed very considerably to the literature on the influence of the emotions on physical conditions. We may mention at random Rokitansky 1849, W. Preyer 1882, A. Sell 1884, Carl Lange 1885, Czerny 1911, Wernstedt 1933, Dunbar 1935, and Schou 1936. Thus psychosomatic medicine is not a new but only a rather neglected branch of medical science.

As a paradigm of a psychosomatic advance may be mentioned the classical case of peptic ulcer, a characteristic, tangible organic disease which, as has been proved in our time, may be caused in a special type of individual (Praeulcusmennesket, Ask-Upmark, 1945) with a tendency to a certain irritability, restlessness, and emotional instability by psychic injury via the sympathico-adrenergic system. The peptic lesion of the intestinal canal is now regarded as only one of the symptoms of the

syndrome of ulcer, and it is purely a matter of chance whether this particular symptom presents itself or not. In about 80 % of the cases the insult causing it has been proved to be of a psychic nature (Davies & Wilson, 1937).

The aim of the present work is to enquire into the occurrence of psychosomatic diseases in a Copenhagen children's hospital during the years 1947—1948.

The Author's Investigations

The Fuglebakken Children's Hospital is a municipal institution of 157 beds, 48 of which are reserved for tuberculous patients, with a turnover of about 1 300 patients a year. Over a 15 months period (1/3 1947—1/6 1948) a total of 464 children over 2 years of age were admitted. The maximum age was 14 years. Out of these, 251 patients were affected by tuberculosis in some form or other and are not included here. This leaves a total of 213 children over 2 years of age.

During the 15 months in question the pathological picture of each single case was considered very carefully for the purpose of determining whether it was dominated by psychic, psychic-social, or somatic components. In practically all cases the author had personal conversations with one or more relatives of the patients in which he went into details as to the case history taken by the intern on duty. The material furnished by the patients was subjected to the current clinical and laboratory examinations.

Under these circumstances it appeared that in 112 out of the 213 children a psychogenic or psychogenic-social factor constituted the essential feature of the pathological picture. In other words: *in 52 % of the children admitted no somatic disease in the stricter sense of the term was found.*

The age distribution of the material is as follows:

Age	No. of Patients
2—3 years	13
3—4 »	16
4—5 »	11
5—6 »	11
6—7 »	16
7—8 »	9
8—9 »	16
9—10 »	9
10—11 »	9
11—12 »	2
	112

For the sake of easy survey the material may be further divided in the following way, though with somewhat indistinct border lines. (In the cases where several symptoms coincide the dominating symptom is mentioned.)

Group I. Actual Psychosomatic Diseases

Enuresis	34
Enuresis + Encopresis	6
Anorexia	17
Abdominal Colic	14
Abdominal Colic + Hypersecretion	4
Encopresis	4
Diarrhoea	4
Constipation	3
Tic	3
Asthma	2
Cephalalgia	1
Neurosis Cordis	1
Vertigo	1
	95

Group II. Disorders of Behavior with Psychic Symptoms

Masturbation	3
Uneasiness and Restlessness	3
Jactitation of the head	1
Nicotinism	1
Pyromania	1
Vagabondism	1
	10

Group III. Constitutionally Organic Diseases with Psychic Symptoms

Debilitas Mentis	3
Adipositas	2
Psychopathy	1
Dyslexia	1
	7

This material serves to corroborate the fact, which, incidentally, is well-known, that *psychosomatic pediatrics constitute a reality in an ordinary, non-specialized pediatric ward*, seeing that in about 1/2 of our patients over 2 years of age we may expect a diagnosis in which psychic causes and somatic manifestations are markedly interwoven, while in only 1/2 may we expect to make an actual organ diagnosis. By way of comparison we may mention Whitehorn's statement that in about 1/3 of all adults seeking medical advice the complaints are almost exclusively of a psycho-neurotic description.

In 4 patients presenting the classical clinical picture of abdominal colic — 3 of whom were suffering so severely that at first they were sent to the surgical ward — considerable hypersecretion in the stomach was demonstrated roentgenologically. All of these 4 patients had been exposed by their surroundings to serious mental injury, and both the pain and the hypersecretion disappeared when the patients were treated with sedatives without any dietetic measures — a beautiful example of psychosomatic disease. The parallelism between these cases and the above-mentioned peptic ulcer is obvious.

Discussion and Conclusion

The progress made in our time is due to the fact that modern laboratory methods of examination have enabled us to show that a normal human being may, if exposed to an emotional trauma, suffer extensive and partly fundamental changes in the organism, the cutaneous glands, the intestinal canal, the blood circulation, and the endocrine glands. Hardly any organ escapes the influence of a psychic trauma, the effect of which may in certain cases be just as radical as that of any physical affection of the organ, an infection or an intoxication (H. J. Schou), so that in all likelihood any mental process will ultimately pro e to issue in a biochemical manifestation (Leland C. Clark). So far these things have not been realized sufficiently, and consequently many physicians are unaware of the fact that the personal problems of a patient often present themselves in a form resembling an organ affection.

This view of psychosomatic relations implies that more reservation should be shown than is customary with many modern psychotherapeutists who one-sidedly attach importance to the psychic trauma only. It is just as incorrect to consider a psychosomatic affection from an exclusively psychic point of view as it was to consider it only from a somatic point of view, as has been the case up till now. We now realize that a fine distinction between psychogenic and somatogenic pathogenesis with regard to several affections in children is misleading. Instead of »either — or» we must consider »both — and». The organism reacts as a whole, regardless of our customary distinction between psychic and somatic factors.

Although the idea of psychosomatic medicine is probably as old as the art of medicine, modern psychosomatic medicine is still in an embryonic stage. To us falls the task of establishing this branch of medical science on a sound scientific basis. In my opinion our immediate efforts should concentrate on the following 3 points.

1. Study of Psychosomatic Relations in Children

We have to admit that hitherto the development of pediatrics has been biased in stressing the somatic affections and their underlying mechanisms, while more or less disregarding the psychogenic factors. It is now urgent to carry on more intensive and comprehensive psychologic and psychiatric studies of children in order to improve their education and care. Our knowledge of these things leaves much to be desired, so much that up to the present the discussion has often turned on the single point of whether the child or the adult is to be the decisive factor. Of course the question should be put like this: do we want to understand the child and recognize its peculiarities? Here lies an almost virgin field for scientific research. The problem may be briefly formulated as an investigation into the influence of the emotions on the physical and mental symptoms of the child.

2. Reeducation of the Personnel in Pediatric Wards

In order to aquire adequate technical aid, it is necessary to disseminate knowledge of diagnostic and therapeutic work among 1) infant pedagogues (*i.e.*, kindergarten teachers), 2) social workers, and 3) professional psychologists. The education of our very most important helpers, 4) the nurses, in the field of child psychology has hitherto been practically nil. If a change is not brought about they will not be able to meet the demands of modern psychosomatic medicine. Further, it is equally necessary to emphasize the importance of child psychology as a part of the education of 5) public health nurses, who, if correctly informed, will prove a great help to parents.

3. Proper Definition of Pediatrics

The material here presented shows that pediatric psychiatric work or, as I prefer to call it, pediatric psychologic work, is no rarity and consequently should not be a speciality within pediatrics, a branch reserved for specially trained psychiatrists, but

an integral part of the knowledge and skill of any pediatrician in exactly the same way as it is expected that a modern-minded physician will be able to form an estimate of the results of biochemical methods in principle (N. B. though he himself may not be able to determine the presence of calcium or cholesterol in serum). This whole aspect of the pathology of childhood — the work connected with pediatric psychology — should not more or less be ignored by the pediatrician. If we fail to carry out what is obviously our duty in this respect the whole domain will fall to the pedagogues and psychologists, who have done some important pioneering work here, it is true, but who cannot, on account of their different education, be expected to possess the knowledge of the pathology of childhood that a physician has. If this division should take place we would probably experience a transition to pure psychotherapy, an alternative which would prove just as fruitless as the exclusively somatic point of view. For these reasons I think that a separation of pediatric psychiatry as an independent special subject within pediatrics would be rather an unfortunate development.

Summary

An examination made in a Copenhagen children's hospital shows that 52 % of the patients over 2 years of age were suffering from psychosomatic affections rather than purely organic lesions. The importance of future work in pediatric psychiatry and psychology is discussed.

Résumé

Un examen fait dans un hôpital d'enfants à Copenhague a montré que 52 % des patients au-dessus de 2 ans souffraient d'affections psychosomatiques plus que de pures lésions organiques. L'importance de futures études de psychiatrie et de psychologie en pédratrie est discutée.

Zusammenfassung

Eine in einem Kopenhagener Kinderspital vorgenommene Untersuchung ergab, dass 52 % der über 2 Jahre alten Patienten

an psychosomatischen Affektionen, vielmehr als an rein organischen Laesionen litten. Es wird die Wichtigkeit der zukünftigen Arbeit in paediatrischer Psychiatrie und Psychologie diskutiert.

Resumen

Un examen efectuado en el Hospital Infantil de Copenhague muestra que el 52 % de los niños de más de 2 años sufrían más de afecciones psicomáticas que de lesiones puramente orgánicas. Se discute la importancia del trabajo futuro de psiquiatría pediátrica y de la psicología.

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(FROM THE FLENSBURG CHILDREN'S HOSPITAL. CHIEF: G. MUHL, M. D.)

Mental Disturbances in Premature Children at School Age

By

BERNHARD BESKOW

Premature infants have shown a tendency to increase in number of late years, a circumstance which places heavy demands on those responsible for the adequate care of these children. Furthermore, the question as to whether these children will develop mentally and physically into perfectly satisfactory individuals gains added significance.

The physical development of premature children has been the subject of several investigations. YLPPÖ has shown that an equalizing process takes place during the first 5—6 years of life, so that on reaching school age these children have caught up to and can afterwards keep up with their fellows of the same age. In Sweden there have been investigations by, among others, von Sydow and G. Muhl. G. von Sydow (1936) established that a certain degree of physical underdevelopment is statistically probable among premature children on reaching school age. Muhl (1939) found that most of the children already had normal weight and height after 3—4 years, a circumstance which she attributed to better nutrition and the prophylactic anti-rhachitic treatment they received.

As regards the psychical development of premature children, there prevails a great difference of opinion. No extensive Swedish investigations of this aspect have been found by the author. G. von Sydow and Muhl could not conclude from their investigations that mental defects were commoner among premature infants than among an unselected material. However, the majority of infants covered by their investigations had not reached school

age and hence no reliable assessment of their mental development could be obtained on account of the short observational period. Most of the studies concerning the mental development of premature children are directly contradictory. GESELL considers that prematurity does not in itself alter the progress of mental development if due account is taken of the premature period. He thinks that in their mental development children follow a cycle independent of external factors. BEITEL concurs with Gesell, but nevertheless he found that 29 % of the premature children in a material of 119 had a lower I. Q. than ordinary children. MOHR and BARTELME showed that of 113 premature infants about 1 were of below average I. Q. Still, they were unable to find any significant difference between these infants and a control group of 40 full-term children. They also found that the mental development of underweight children was as good as that of those with a higher birth weight. MARY CROSSE is of the opinion that the majority of premature children undergo normal mental development if due allowance is made for the premature period. The same view has been adopted by LEVINE and GORDON as well as HESS in the U. S. A. On the other hand, CAPPER, who studied 437 children in the year 1928, found that premature children develop later than normal children as regards sitting, standing, walking and talking. He found that the organs were not adequately developed for their functions, that the premature infants were incapable of leading an independent extra-uterine life, and that they exhibited a high frequency of birth lesions. ROSANOFF and INMAN-KANE found that among 122 patients at an institute for oligophrenics 21.3 % had been born prematurely and were immaturely developed. The corresponding figure shown by the control group was 3.89 %. Among 146 premature children who had reached school age mental disturbances were found in 15, or 10.27 %. In an unselected control group the corresponding figure was 2.63 %. PARVIAINEN (1945) found that premature children born with breech presentation had a specially high mortality and that the mental development of the survivors was very poor (mental underdevelopment in 25 %). In those cases in which there had been recourse to high forceps extraction as well as in

those with inner correction and extraction the I. Q. values were bad. BRANDER, in his investigations of premature children 6 to 15 years of age, found an I. Q. below 70 in 11.2 % (the children were examined by the Binet-Simon method). In a group free from hereditary taint and cerebral lesions he found a value of 4.3 %. In a group with parturient complications but without hereditary taint the value was 13.6 %. When he took account only of hereditary tendencies but not of birth complications, he found oligophrenia in 24.1 %. The highest figure, 35 %, was however found in the group with both partus complications and hereditary taint. Even in the absence of these two factors, however, Brander considered subnormal birth weight to play a considerable part in underdevelopment of intelligence among the premature; in a material of 230 cases he observed that the lower the birth weight, the more underdeveloped the intelligence. Cerebral haemorrhages, forceps deliveries, breech presentations and twin deliveries constitute great elements of risk for prematurely-born children. BENTON claims that these children acquire nervous disorders to a very marked extent, but interprets these as due more to social conditions than prematurity in itself.

From this short survey it will be seen that opinions are very divergent. Moreover, investigations of the mental development of premature infants are few in number, and in most of them the period of observation is insufficiently long to ensure safe judgment of the test results. There are great difficulties in the way of securing a sufficiently large material of premature children and of following them up for a sufficiently long period during their development. So-called pseudo-oligophrenia may easily occur, as premature children very often have isolated disturbances in the central nervous system or the organs of sense. Above all, their speech development is frequently slow and poor and if this is not taken into account their I. Q. may be recorded as low. In these cases, therefore, an analysis of the test results is necessary, and these children ought to be controlled at intervals of about one year.

To study these conditions the author has followed up a number of children with birth weight under 2 500 g who were born in

the Maternity Department of the Malmö General Hospital and afterwards attended at the Flensburg Children's Hospital. The material comprizes 289 children born between the years 1929 and 1939, and a further 16 children who went directly from the Maternity Department to their homes. These last-mentioned were included for the sake of completeness and 9 of them were attended later at the Flensburg Children's Hospital. Hence the whole material covers 305 children, 135 boys and 170 girls. The children have either been examined personally by me or I have been able to follow them through the Psychical Advisory Centre of the Schools, the material of which has kindly been placed at my disposal by its chief, Dr. V. Varde. Of the 305 children, 32 dropped out for various reasons — only 10.5 %. 19 moved from the town, 8 died after discharge from the hospital (among these 2 mongoloid idiots, 1 boy and 1 girl, and 1 boy with hydrocephalus) while 5 children could not be found. Thus there remain 273, 123 boys and 150 girls. During the period 1929—1939, 35 of the premature children admitted to the Flensburg Children's Hospital died, these consisting of 19 boys and 16 girls, and hence the immediate mortality is 12.11 %. The children who died are distributed according to their birth weights in the Table 1 below.

Table 1.

Birth Weight	No. of Boys	No. of Girls
1 000—1 500 g	12	7
1 510—2 000 »	5	7
2 010—2 500 »	2	2
1 000—2 500 g	19	16

It will be seen from the Table that most of the dead children belong to the groups that had the lowest birth weight, this being markedly the case among the boys. For boys and girls the commonest cause of death was acute bronchitis, which according to clinical and post-mortem findings 10 boys and 8 girls had. As a rule these infants died between the 3rd and 4th months of life; only 4 of the boys and 1 of the girls died within the first week.

Cerebral haemorrhage was responsible for the death of 3 girls and 3 boys, for whom the average time of death was the 5th day of life, and none of these babies died later than the 7th day, 2 babies, 1 boy and 1 girl, had vitium congen. cordis and both these children succumbed within a fortnight of delivery. The other causes of death were chiefly infections, 1 boy died of pyonephrosis, 1 boy and 2 girls of sepsis, and 1 boy and 1 girl had erysipelas. All of these last-mentioned children passed away between the first and second months of life. In 3 cases autopsy revealed no contributory cause of death beyond the prematurity, and as a matter of fact the birth weights were low in these, being between 1 000 and 1 200 g. How the 273 surviving children are distributed over the different weight groups is evident from Table 2.

Table 2.

Birth Weight	No. of Boys	No. of Girls
1 000—1 500 g	22	30
1 510—2 000 »	57	58
2 010—2 500 »	44	62
1 000—2 500 g	123	150

Among the children are 16 surviving pairs of twins and 15 twins whose fellows died.

The most important object of the investigation has been to study how the surviving children got on at school. They were tested at the Psychical Advisory Centre of the Schools by the assistants there and in a number of cases by the author. The tests were carried out by Terman's method, according to the Terman-Merrill Form L and in a small number of cases Form M. As a rule they were tested at intervals of 1 year, an analysis of the test results being made in each case. The period during which the children were under observation is satisfactory, since none of those tested was under 9 years of age and the eldest was 17. Of the 273 children, no fewer than 68 were referred to the Psychical Advisory Centre on account of difficulties at school of some kind or the other — almost 25 %. Of these, 39 were boys and 29 were

girls. The school difficulties were caused by inability to keep up with the class and nervous disorders in 49 cases, difficulties in reading in 3 cases, and pronounced nervous symptoms in 16. When an assessment is being made of the test results, it should be borne in mind that maturity for starting school is considered to demand an I. Q. of above 90. Otherwise the children are generally granted 1 year's postponement of school attendance. Children with an I. Q. between 70 and 80 attend a relief class. Those having an I. Q. below 70 are in Malmö transferred to the day-school for educable mentally defective children at Värnhem and those having an I. Q. between 50 and 60 to a boarding-school at Håkanstorp. Experience shows that schooling troubles are also found among children whose I. Q. is between 85 and 90. As a rule these children have to attend the so-called B classes, as it has been found that they cannot keep up with the ordinary classes, where they fail to get promotion and cause the normal I. Q. children trouble of different kinds. Of all the school-children in the town of Malmö, it is estimated that between 15 % and 20 % are Class B scholars. The number of relief class children varies somewhat, keeping as a rule between 2.5 % and 3.3 %. In addition Malmö has an observation class for problem children and special classes for children suffering from poor hearing, speech impediments, stammering, and word-blindness.

Out of the whole material, 44 children had an I. Q. below 85. The distribution of these children over the different groups was as follows.

Table 3.

Birth Weight	No. of Boys	%	No. of Girls	%
1 000—1 500 g	4	18.1	7	23.3
1 510—2 000 »	9	15.7	7	12.1
2 010—2 500 »	8	18.1	9	14.5
1 000—2 500 g	21	17.0	23	15.3

These children constitute 16.11 % of the whole material.

If the children whose I. Q. was less than 60 are taken separately the following distribution is obtained.

Table 4.

Birth Weight	No. of Boys	No. of Girls
1 000—1 500 g	0	3
1 510—2 000 »	3	2
2 010—2 500 »	1	4
1 000—2 500 g	4	9

Expressed in percentages of the total number the figures will be 3.25 for the boys and 6.0 for the girls. Altogether, 13 children had an I. Q. of less than 60, forming 4.76 % of the material. Of these 2 were sent to the boarding-school at Håkanstorp and 10 to the day-school for educable mental defectives. The latter constitute 1/3 of all the children there. One boy whose I. Q. was between 30 and 35 was ineducable. Deducting this case, the mean I. Q. of these children was 53 for the boys and 57 for the girls. Among the children in the relief classes the mean I. Q. for the boys was 78 and that for the girls was 75. During the legal school years for these children the number of relief class members among the total number of school-children in Malmö averaged 2.55 %. The number of children in our material attending B classes was uncertain, as the division into A and B classes has been undertaken only during recent years. However, of the children born in 1938 and 1939, about 20 % of the boys and 18 % of the girls in the material were assigned to the B class, as would normally be expected. Their I. Q. averaged about 90 for the boys and about 91 for the girls.

As was previously mentioned, birth complications were very common among the premature children and included a high number of cerebral haemorrhages. The distribution of this latter complication among the surviving children in the material is recorded in Table 5. All these cases had undoubted clinical signs of intracranial haemorrhage with a tense fontanelle, cyanotic attacks, lethargy, sometimes changes of the tonicity in arms and legs as well as positive lumbar puncture finds. None of them had paresis. Hence 18 children had undoubted cerebral haemorrhages after partus, *i. e.* 6.59 % of the whole material, or 8.1 % for the boys and 5.33 % for the girls, this complication thus being considerably

Table 5.

Birth Weight	No. of Boys	No. of Girls
1 000—1 500 g	3	3
1 510—2 000 »	4	3
2 010—2 500 »	3	2
1 000—2 500 g	10	8

commoner among boys than among girls. From Table 5 it will be seen that the number of cerebral haemorrhages was not greater among the children with a low birth weight than among those with the highest in the material.

In a study of children having a low I. Q. account must naturally be taken of the hereditary factors present in those cases in which one or both of the parents has been mentally deficient. Disregarding these cases in the material as well as those that had postnatal haemorrhages of the brain, we obtain the following distribution of those children whose I. Q. was less than 85.

Table 6.

Birth Weight	No. of Boys	No. of Girls
1 000—1 500 g	1	4
1 510—2 000 »	4	3
2 010—2 500 »	4	7
1 000—2 500 g	9	14

These children total 23, 8.42 % of the total material.

Table 7 below shows the distribution over the different weight groups of the mean I. Q. of those children in the whole material whose I. Q. was below 85.

Table 7.

Birth Weight	No. of Boys	Mean I. Q.	No. of Girls	Mean I. Q.
1 000—1 500 g	4	76	7	69
1 510—2 000 »	9	70	7	68
2 010—2 500 »	8	76	9	67
1 000—2 500 g	21	74	23	68

If the cases in which there were postnatal complications in the form of cerebral haemorrhages or in which hereditary factors played a role are ignored, the distribution assumes the following appearance.

Table 8.

Birth Weight	No. of Boys	Mean I. Q.	No. of Girls	Mean I. Q.
1 000—1 500 g	1	71	4	75
1 510—2 000 »	4	81	3	71
2 010—2 500 »	4	77	7	70
1 000—2 500 g	9	76	14	72

These tables indicate that the mean I. Q. is somewhat lower in those cases in which undoubted cerebral haemorrhages occurred or in which hereditary factors played a part than in the others. It is also evident from the tables that the I. Q. was not lower in the low birth weight cases than in the higher. While this does not agree with Brander's view referred to above, it seems to agree well with the results arrived at by Mohr and Bartelme.

The most constant symptom in the children who had cerebral haemorrhages was *cyanotic attacks*, from which all of them suffered. Attacks of cyanosis also appeared in a further 10 cases of the surviving children. In these a cerebral haemorrhage was not clinically suspected. Only 3 of these 10 children got on well at school. The rest consisted of 2 children (1 boy and 1 girl) whose I. Q. was less than 85 and who attended relief classes, 3 boys who were sent to health classes on account of pronounced nervous symptoms, all of whom had an I. Q. of about 90, and 2 children who attended B classes. From these data it will be seen that cyanotic attacks ought to be regarded as a bad prognostic sign, both for the immediate future — since complications from the brain or the lungs are most frequently the cause of these attacks — and for later developments. A glance at the weight curves shows that during the first period of life these infants do not increase in weight so much as the other children. This is especially evident during the first month of life, since after that they generally show an improvement in weight, as is indicated by more especially those weight curves set up before stomach-tube feeding was introduced

more regularly for the low-grade children. The fact is that these infants are apathetic, difficult to feed, keep the food in their mouths, and have frequent vomitings.

In the whole material there were 19 cases of *breech presentation*, 11 for boys and 8 for girls. Among these, 2 boys and 2 girls had cerebral haemorrhages, and all of these infants were assigned to relief classes except 1 boy, who was ineducable and whose I. Q. was 30—35. Another 2 boys and 1 girl had a somewhat low I. Q. of about 90, and all these were sent to the B class. Hence 7 of the children with breech presentations, *i. e.* over 1/3 of all, had a sub-normal I. Q.

In no case in the material was it necessary to have recourse to a mid or high forceps operation for delivery, but in 9 cases *Naegele's forceps* was used, in 6 cases on boys and in 3 on girls. In none of these cases was it necessary for the child to attend relief classes, though 2 of the boys, with an I. Q. of 85 and 90 respectively went to B classes. All the other children got along excellently in normal classes. It is accordingly seen that these forceps extractions did not make the prognosis worse for these children, and no complications from the brain were recorded.

The number of twins in the material is relatively large, comprizing 16 surviving pairs and 15 twins whose fellows died immediately after partus or (in 6 cases) were dead before partus. The immediate mortality of these children is accordingly high. Of the surviving twin pairs there was only 1 which later attended a relief class. The I. Q. of these 2 was 77 and 85 respectively. Among the single surviving twins 3 attended relief classes, 2 were sent to health classes on account of nervous symptoms, but all the others showed a normal I. Q. Of the total number of 47 twins there were thus 5 that had an I. Q. below 85, *i. e.* a frequency of about 10 %, which is fairly high. These children, however, had no fewer than 3 cerebral haemorrhages and in 1 case both the parents were mentally deficient. Hence it is the complications associated with paturition that play a great part for the twins and their future development.

An analysis of the whole material as regards the time at which the children *began to walk* gives the following distribution.

Table 9.

Birth Weight	No. of Boys	Walked at (Average)	No. of Girls	Walked at (Average)
1 000—1 500 g	22	15 mths.	30	15 mths.
1 510—2 000 »	57	13 mths.	58	13 mths.
2 010—2 500 »	44	12 mths.	62	13 mths.
1 000—2 500 g	123	13 mths.	150	13 mths.

The tabulated data show that on an average the infants in the lowest weight-class, 1 000 to 1 500 g, began to walk 2 months later than the others.[1] A similar analysis of those children whose I. Q. was less than 85 gives the following distribution.

Table 10.

Birth Weight	No. of Boys	Walked at (Average)	No. of Girls	Walked at (Average)
1 000—1 500 g	4	20 mths.	7	21 mths.
1 510—2 000 »	9	17 mths.	7	18 mths.
2 010—2 500 »	8	17 mths.	9	20 mths.
1 000—2 500 g	21	18 mths.	23	19 mths.

Taking those children separately whose I. Q. was less than 85 but who were free from injuries of the brain or hereditary taints, we obtain the following table.

Table 11.

Birth Weight	No. of Boys	Walked at (Average)	No. of Girls	Walked at (Average)
1 000—1 500 g	1	16 mths.	4	15 mths.
1 510—2 000 »	4	17 mths.	3	16 mths.
2 010—2 500 »	4	15 mths.	7	15 mths.
1 000—2 500 g	9	16 mths.	14	15 mths.

These tables clearly show that on an average these children begin to walk somewhat later than normal, but that this finding is influenced by the cases with brain injuries or hereditary taints.

[1] In a control group of 50 children both the boys and the girls commenced to walk and talk in their 12th month.

A similar analysis of the whole material with regard to the time at which the children *began to talk* gives the following result.

Table 12.

Birth Weight	No. of Boys	Talked at (Average)	No. of Girls	Talked at (Average)
1 000—1 500 g	22	16 mths.	30	16 mths.
1 510—2 000 »	57	15 mths.	58	14 mths.
2 010—2 500 »	44	14 mths.	62	13 mths.
1 000—2 500 g	123	15 mths.	150	14 mths.

According to this table, the children commence to talk somewhat later than is normal, mainly in the lowest weight-group. Separate analysis of the children having an I. Q. below 85 yields the following distribution.

Table 13.

Birth Weight	No. of Boys	Talked at (Average)	No. of Girls	Talked at (Average)
1 000—1 500 g	4	30 mths.	7	26 mths.
1 510—2 000 »	9	24 mths.	7	25 mths.
2 010—2 500 »	8	24 mths.	9	22 mths.
1 000—2 500 g	21	26 mths.	23	24 mths.

Taking separately the children with no cerebral injuries or unfavourable hereditary tendencies, we obtain the following distribution.

Table 14.

Birth Weight	No. of Boys	Talked at (Average)	No. of Girls	Talked at (Average)
1 000—1 500 g	1	20 mths.	4	20 mths.
1 510—2 000 »	4	20 mths.	3	19 mths.
2 010—2 500 »	4	20 mths.	7	18 mths.
1 000—2 500 g	9	20 mths.	14	19 mths.

From these tables it is clear that children with brain injuries, unfavourable heredity or otherwise having a low I. Q. begin to speak later than normal infants.

An examination of the whole material to ascertain at what age the children are able to *keep dry* both during the day and the night has given the following result.

Table 15.

Birth Weight	No. of Boys	Dry at (Average)	No. of Girls	Dry at (Average)
1 000—1 500 g	22	5 yrs.	30	4 yrs.
1 510—2 000 »	57	4 yrs.	58	3 yrs.
2 010—2 500 »	44	3 yrs.	62	3 yrs.
1 000—2 500 g	123	4 yrs.	150	3 yrs.

If the analysis is restricted to the children whose I. Q. was less than 85 the result is as follows.

Table 16.

Birth Weight	No. of Boys	Dry at (Average)	No. of Girls	Dry at (Average)
1 000—1 500 g	4	5 yrs.	7	4 yrs.
1 510—2 000 »	9	5 yrs.	7	4 yrs.
2 010—2 500 »	8	4 yrs.	9	3 yrs.
1 000—2 500 g	21	4 yrs.	23	3 yrs.

Exclusion of the cases with cerebral injuries or hereditary taint gives the following distribution instead.

Table 17.

Birth Weight	No. of Boys	Dry at (Average)	No. of Girls	Dry at (Average)
1 000—1 500 g	1	4 yrs.	4	4 yrs.
1 510—2 000 »	4	4 yrs.	3	4 yrs.
2 010—2 500 »	4	4 yrs.	7	3 yrs.
1 000—2 500 g	9	4 yrs.	14	3 yrs.

From the tables it will be seen that children who had brain injuries or in whom hereditary factors played a role learnt to keep dry later than normal ones. The girls started to keep dry earlier than the boys.

As mentioned earlier, in the case of children who were found unable to keep up with a normal class during their first school year and who had a low I. Q. it was very common for leave of absence from school to be granted for one year in order to see

whether they could develop by the next school year. Of the children whose I. Q. was less than 85 in the material, 19 of the 21 boys were allowed a postponement of school attendance and 20 of the 23 girls. Among those granted postponement were all who had cerebral injuries or cyanotic attacks except 2. The reasons for non-attendance were (I) deficient mental development, (II) general infantilism, the children still being mentally in the age of play and unable to interest themselves in study and school work.

In the material 2 children, 1 girl and 1 boy, had epilepsy. Delivery was, however, normal in both these cases, the babies exhibited no postnatal lesions, and their earliest development was normal. In these cases, therefore, the debility could scarcely have played any part in these diseases. Among the other children who had been subject to birth complications and the children who undoubtedly suffered cerebral haemorrhages, 5 boys and 4 girls exhibited symptoms of injuries to the central nervous system at school age. The male incidence was 4.0 % and the female 2.6 %, *i. e.* almost double as high a frequency for boys. None of these children had an I. Q. above 80. 2 girls and 1 boy had an I. Q. between 50 and 60. Of these, 1 boy and 1 girl were sent to the residential school for mentally defective children (Håkanstorp) and 1 girl went to the special day-school for such children. All the other children attended relief classes. 3 boys and 1 girl had symptoms of injuries to the brain in the form of spastic paresis of the Little type in both legs and 2 boys and 3 girls had unilateral spastic paresis. The others manifested no gross symptoms of lesions to the central nervous system in the form of reflex changes. A distribution by birth weight follows of the children who displayed neurological disturbances.

Table 18.

Birth Weight	No. of Boys	Total No. of Brain Injuries	No of Girls	Total No. of Brain Injuries
1 000—1 500 g	2	3	2	3
1 510—2 000 »	1	4	2	3
2 010—2 500 »	2	3	0	2
1 000—2 500 g	5	10	4	8

It appears from this table that half of the children who had cerebral haemorrhages at partus displayed at school age gross neurological symptoms of injuries in the form of spastic paresis. It is also seen that the children who had a birth weight between 1 000 and 2 000 g. exhibit neurological symptoms more frequently than the other children.

Slow and poor development of the power of speech was a frequent finding among the premature children. At school age different groups could be distinguished, *viz.* stammerers, lispers, and slurrers. The last-mentioned had difficulties in forming words, talked thickly, or ran their syllables together and were generally difficult to understand. The following tables show the incidence of these disturbances in speech. Table 19 gives the number of cases of speech disturbances observed in the whole material.

Table 19.

Birth Weight	No. of Stammerers		No. of Slurrers		No. of Lispers	
	Boys	Girls	Boys	Girls	Boys	Girls
1 000—1 500 g	3	3	2	3	2	2
1 510—2 000 »	5	5	8	3	1	2
2 010—2 500 »	4	2	4	4	1	4
1 000—2 500 g	12	10	14	10	4	8

For that part of the material whose I. Q. was less than 85 the incidence was as follows.

Table 20.

Birth Weight	No. of Stammerers		No. of Slurrers		No. of Lispers	
	Boys	Girls	Boys	Girls	Boys	Girls
1 000—1 500 g	3	3	2	3	2	2
1 510—2 000 »	5	5	8	3	1	2
2 010—2 500 »	4	2	4	4	1	4
1 000—2 500 g	12	10	14	10	4	8

4 girls and 2 boys had all the above disturbances of speech. A separate analysis of the children whose I. Q. was less than 85 but who had not suffered from cerebral injuries or hereditary taint gave the following result.

Table 21.

Birth Weight	No. of Stammerers		No. of Slurrers		No. of Lispers	
	Boys	Girls	Boys	Girls	Boys	Girls
1 000—1 500 g	0	0	0	0	0	2
1 510—2 000 »	0	1	2	1	0	1
2 010—2 500 »	2	2	1	1	0	2
1 000—2 500 g	2 (22 %)	3 (21 %)	3 (33 %)	2 (14 %)	0	5 (35 %)

From the tables it is seen that the majority of children afflicted with the above-mentioned disturbances of speech belong to those groups in which there were cerebral injuries or hereditary taint.

In the whole material, 25 boys (20.3 %) and 24 girls (16.0 %) failed to pass »counting» during the first school year. Almost all of these children belonged to those who had a low I. Q. Of those whose I. Q. was below 85, only 1 boy and 2 girls passed. Thus 80 % of the boys and 87.5 % of the girls who failed had an I. Q. below 85. Not a single child among those with cerebral injuries at partus was passed and none of them was able to solve a sum without assistance within the 1—10 range. Mental counting was the most difficult task for these children, and all of those with an I. Q. below 85 had to use their fingers as a help. Those children who attended the day-school for mental defectives had much difficulty in acquiring a sense of number. These infants all had an I. Q. between 50 and 60. As a rule, however, after a couple of terms they learnt the simplest elements of counting.

As regards writing, 50 % of the children whose I. Q. was below 85 had considerable difficulties and about 35 % found it somewhat easier. The writing ability of the remaining 15 % was fairly good. To the first group, *viz.* those who found writing most difficult, belonged all who had cerebral injuries. These children were extremely fumbling and awkward in their manipulation of the pen or pencil and had difficulty in shaping letters, which were usually given a clumsy and misshapen appearance. Some of the children regularly reversed the order of the letters. They generally managed copying work better than other tasks and ordinary handwriting better than printed letters. Free handwriting was

not managed so well as copying. These children had poor powers of concentration and but little perseverance. They quickly became tired, and, as BRANDER has shown, they also had poorly functioning muscles. In the whole material there were 11 boys and 8 girls who were left-handed, corresponding to 8.9 % of the boys and 6 % of the girls. This is a normal number, since between 5—10 % of all school-children are expected to be left-handed. Amongst those in our material whose I. Q. was less than 85 there were 4 left-handed boys and 2 left-handed girls, and of these only 1 boy had a cerebral injury at birth. From these figures it is accordingly seen that in our material brain injury was not associated with a higher degree of left-handedness, nor was this to be expected.

Ability to read is, of course, intimately bound up with the development of the power of speech. Tables 19, 20, and 21 show that a high percentage of the children exhibited developmental disturbances in speech, more especially those with a low I. Q. Among the children in the material whose I. Q. was below 85, between 50 % and 60 % were able to read. As a rule they learnt letters and sounds fairly quickly but then had much difficulty in combining the sounds into words. Gradually they learnt to read simpler words, but when longer words were attempted they broke down. If they became nervous or tired, the result was of course wretched, and here too their abnormal fatigability made itself felt. Frequently they did not understand how to divide words into syllables. It was also very typical of them that they did not understand what they read; they had a poor idea of the subject-matter and could not give an account of it. They also misunderstood simple actions, and so on.

Patients with a low I. Q. are often considered to have relatively well-developed practical mechanical skill. To ascertain whether this also applied to premature infants, the author studied the material from this aspect. In school mechanical skill is tested chiefly in manual training (slöjd), sewing, drawing, painting, and gymnastics. Among the children with an I. Q. below 85, 11 boys were poor in gymnastics and slöjd an 7 very bad. Only 3 boys were good in these subjects. Among the girls 14 were poor in

the corresponding subjects and 5 very poor, only 4 being good. They sewed and cut badly, fumbled about, and could not concentrate on the simplest tasks. Nor could they draw objects and were often seen to draw them upside down — houses, for example. In gymnastics it was often noticed that these children were feeble and that their muscles functioned badly; they had difficulty in controlling their arms and legs, as was manifested by the fact that they ran badly, often tumbled, and so on. Frequently it was found that they had less control of one leg than the other; the poorer leg dragged behind the other, etc. None the less, no reflex disturbances were discovered on neurologic examination. Those afflicted with cerebral injuries at partus were among the worst.

The children with an I. Q. below 85 often demonstrated deficient concentration and attention at school and during the tests. Of the 21 boys, 17 were absent-minded, and of the 23 girls, 14. Only 4 boys and 9 girls displayed normal attention. The others showed no interest in the teaching, stared out of the window, leant their heads against the desks, or talked loudly, sang, or laughed without reason. They were not captivated like normal children by tales and understood little of the subject matter. Some of these children ran about during the lessons, looked into the books of other children, wrenched the books from them, etc., all of which made them a very disturbing element in the class.

The teachers denoted the memory of 19 of the 21 boys and of 20 of the 23 girls as bad. 10 of the 44 children whose I. Q. was below 85 were described as being even-tempered, *viz.* 3 boys and 7 girls. The other children showed an uneven temper at school; they were changeable, violent, and irascible. This brings us to their nervous troubles, and of the children with an I. Q. under

Table 22.

Birth Weight	No. of Boys	Nervous	%	No. of Girls	Nervous	%
1 000—1 500 g	4	3	75	7	6	85.7
1 510—2 000 »	9	9	100	7	7	100
2 010—2 500 »	8	8	100	9	8	88.8
1 000—2 500 g	21	20	95.2	23	21	91.2

85 the majority had pronounced nervous symptoms. This can be clearly seen from Table 22, which shows the frequency of nervous disturbances in all children whose I. Q. was less than 85.

If the children with cerebral haemorrhages or hereditary taint are excluded, we get the following table instead.

Table 23.

Birth Weight	No. of Boys	Nervous	%	No. of Girls	Nervous	%
1 000—1 500 g	1	0	—	4	3	75
1 510—2 000 »	4	4	100	3	3	100
2 010—2 500 »	4	4	100	7	6	85.7
1 000—2 500 g	9	8	88.8	14	12	85.7

From these tables it is evident that nervous disturbances are extremely common among these children. They are also common among the other children in the material who had an I. Q. above 85. It is an old experience that a high percentage of premature children have nervous disorders. For instance, in a material from a children's Care Centre, BESKOW found that premature infants showed nervous symptoms in about 66 % of the cases during the first few years of life. In our material about 50 % of the children displayed nervous disturbances, the same percentage for both boys and girls.[1] However, as is indicated by Tables 22 and 23 above, it is mainly the children with a low I. Q. who had nervous disorders, above all those who had cerebral haemorrhages at birth or in whom there were hereditary taints.

The nervous symptoms of the neurotic children were much alike as a rule, and therefore a brief mention of some typical features will suffice. Even when the children had reached school age they reacted like babies: they were mentally and physically infantile. Even when small they evinced a *primitively unchecked need for movement* which they retained during the first few school years. They often exhibited high-grade motor unrest and were as »lively as quicksilver», practically never still. Frequently they were restless, could not sit still at school, stuck out their fingers,

[1] In a control group of 50 children there were nervous symptoms in about 30 %.

twisted their bodies about, gesticulated, laughed to themselves without reason, pulled wry faces, turned round on their seats, talked loudly, or sang. Their movements were not regular and balanced but jerky and twitchy. These children often jumped up during lessons and their peculiar actions had a very disturbing effect on the work of instruction. Such symptoms were more or less pronounced in 95 % of the nervous boys and in 90 % of the girls. *Tic* occurred in about 40 % of the cases, *obsessions* in about 30 %, *thumb-sucking* and *nail-biting* in about 35 %.

Emotional lability was also a very prominent feature in these children. This came to expression in uncontrolled and violent attacks of passion. The mental equilibrium of these children was very easily upset and they then often became wild and bewildered in their actions, lost self-command, fought, scratched, kicked, spat and stamped on the ground, shouted violently, threw things about them and even threatened those around with knives. This last applies to several cases in the present material. They were also very sensitive to vocal cadence and were apt to weep even in response to quite gentle admonitions. As a rule their attacks passed over quickly, and only in exceptional cases were the children revengeful or given to nursing grievances. Emotional lability was the commonest symptom exhibited by these children, having been registered in 95 % of both the boys and girls. Here too, of course, the intensity of the symptoms varied. On the other hand, *absence of emotion* (apathy), *i. e.* a shallow or superficial emotional life, was noticed in several cases.

The *ethical sense* was rather late in maturing in these children: they thought most of play during the first few school years and could not understand the purpose of school instruction. They often found it difficult to agree with their school mates, especially those of the same age. Most of them got on better with smaller children who yielded to them. The boys in the material tended to quarrel with their school mates in about 80 % and the girls in about 60 % of the cases. Approximately the same figures apply to siblings.

The children were frequently slow thinkers and found it hard to concentrate on questions and tasks. *Deficient power of*

concentration in these children was recorded in 85 % of the nervous boys and in about 75 % of the girls. *Increased fatigability* was also typical and occurred in 90 % of both the nervous boys and the nervous girls. This manifested itself in, among other things, their being utterly exhausted when they left school. Many had to go to bed; others merely cried. Rather many (about 10 %) of the children complained of *headache* on arriving home from school. *Disturbances in sleep* occurred in about 20 % of the children and *refusal to eat* or *nervous gastric disorders* in about 15 %, about equally often among boys and girls. *Phobia* was found in about 10 % and mostly took the form of dread of the dark or of being alone. *Truancy* from school occurred only in a few cases and no certain case of »aversion» or sheer laziness could be established. *Pilfering* was discovered in a couple of cases.

An *excessively strong subjection* to a person of authority, *i. e.* an infantile attitude, was very common and may be estimated as present in between 80 % and 90 % of all. As a rule, the person of authority was the mother. More rarely, it was the father or in a few cases the teacher of the class or some classmate who had taken the child concerned in hand. A common finding was that the mother had to feed and dress the child up to an advanced school age.

Sexual peculiarities occurred in only 2 cases of the material, which is a very small proportion. It also looked as though puberty would set in somewhat later in these premature children than in normal ones.

Very often these children showed a waiting attitude, and when they reached an age of 8—10 years they were often markedly *subvalid*: everything had to be arranged for them in the customary way, and so on. This trait occurred in between 80 % and 90 %. Not uncommonly they fell into a state of depression easily, sometimes becoming thoroughly despondent. They might accordingly often exhibit signs of *substability*, and when they reached 10—12 years of age these traits could be distinguished in about 50 % of the cases. In many of these children it was possible to distinguish alternating moods of depression and exultation.

Summarizing the above-mentioned findings, it may be said that the nervous disorders of premature children are often very typical and that these children show a characteristic mode of reaction. They are mentally and physically infantile, frequently exhibit excessive subjection to a person of authority, show late development of the ethical sense, have a primitive unrestrained need for movement, are emotionally often extremely labile, and display poor power of concentration and excessive fatigability.

The *social conditions* of the children composing the present material were very bad. A very large proportion of them were born out of wedlock, in all about 60 %. In 6 cases provocative interferences had occurred. The social conditions were very bad in about 10 % and there was abuse of alcohol in about 12 %. Barely 1/2 of the children came from an irreproachable environment. The children born in wedlock proved to have less nervous trouble than the others, the percentage being about 35, and these children showed better progress at school than the others. Some of the children included in this material have left school and started in life. Of the eldest batch, *i. e.* those born in the year 1929, 1 is dead and 4 have moved to other towns. Among the others, there are 5 shop-assistants, 2 office-clerks, 1 waitress, 1 meat-cutter, 8 factory-workers, and 2 apprentices, 1 of whom is engaged in silversmith's work and 1 in another handicraft. All of these have hitherto been free from any serious symptoms of mental insufficiency and seem to be getting on well.

From this investigation it is evident that premature children seem to develop somewhat later than normal ones both as regards the time at which they begin to walk and talk and in the development of intelligence. The analysis of the material shows, however, that this mainly depends upon (I) hereditary taint, *i. e.* mental deficiency in the parents, (II) injuries to the brain at partus. The debile children are evidently very apt to incur such injuries, and this is a great risk in complicated deliveries, such as breech presentations twin deliveries. Children who have suffered cyanotic attacks behave on the whole like those who have had undoubted clinical haemorrhages of the brain, and it is obviously quite pos-

sible that they have also had such haemorrhages. If these cases are left out of account, it is found that premature children develop like normal children, although they are subject to nervous disorders and disturbances to a greater extent than these. Such disorders, however, appear to be compensated for in time, above all as a result of a proper understanding and adequate treatment. The number of brain injuries must be brought down, but here, of course, the specialist for children's diseases is more or less powerless, and it is the obstetrician who has an important field of work.

Summary

The material comprises 273 premature children. They were tested between 9 and 15 years of age and 16.11 % had I. Q.'s below 85. Those who had cerebral haemorrhages during the first post-partum period (6.59 %) experienced the greatest difficulty in getting on at school and had the lowest I. Qs.'. Throughout the material the children commenced to walk and talk later than children belonging to an unselected control group and were likewise inferior to normal children in their mental development. When those who had suffered post-partum haemorrhages of the brain or cyanotic attacks and those whose parents were mentally deficient were left out of account, however, it was found that development was normal. 1/2 of the children who had had cerebral haemorrhages showed spastic paresis at school. About 50 % of the children in the material had nervous symptoms (in a control group taken at random the figure was about 30 %). Children who have suffered cyanotic attacks behave like those who have had cerebral haemorrhages. If these cases are left out of consideration, it is found that premature children develop like normal ones, although they get nervous disorders to a greater extent than the latter.

Résumé

Notre objet d'étude comprend 273 enfants nés avant terme, examinés aux âges de 9—15 ans; 16.11 % d'entre eux avaient un Q. I. au-dessous de 85, et 6.59 % ont eu des hémorragies

cérébrales après le partus, ils ont eu le plus faible Q. I. et le plus de difficulté à suivre les leçons à l'école. La moitié de ces derniers ont eu des parésies spatiques à l'âge d'aller à l'école. Il en était de même pour ceux qui avaient eu des attaques de cyanose. Abstraction faite des enfants qui ont eu des hémorragies cérébrales ou des attaques de cyanose ou bien des parents hébétés, les enfants de notre objet d'étude se sont développés comme les enfants d'un groupe de contrôle quelconque, mais plus lentement; ils ont marché et parlé plus tard, leur développement psychique était moins bon et surtout ils avaient un plus grand nombre de troubles nerveux: 50 % des enfants de notre objet d'étude au lieu de 30 % de ceux d'un groupe de contrôle quelconque.

Zusammenfassung

Das Material umfasst 273 frühgeborene Kinder. Bei einer Testung im Alter von 9—15 Jahren hatten 16,11 % einen I. K. unter 85. Die Kinder, welche nach der Geburt Gehirnblutungen hatten (6,59 %), kamen in der Schule am schwersten weiter und hatten den niedrigsten I. K. Alle Kinder des Materiales begannen später zu gehen und zu sprechen als die Kinder einer nicht ausgesuchten Kontrollgruppe und zeigten eine schlechtere psychische Entwicklung als normale Kinder. Abgesehen von den Kindern, die Gehirnblutungen oder Cyanose-Anfälle gehabt hatten oder deren Eltern geistesschwach waren, entwickelten sich alle wie normale Kinder. Die Hälfte von denen, welche Gehirnblutungen hatten, bekamen im Schulalter spastische Paresen. 50 % der Kinder des Materials hatten nervöse Beschwerden gegenüber 30 % der Kontrollgruppe. Die Kinder mit Cyanose-Anfällen verhielten sich wie die mit Gehirnblutungen. Abgesehen von diesen entwickelten sich also die frühgeborenen Kinder wie normale, wenn sie auch häufiger nervöse Beschwerden bekamen.

Resumen

El material abarca 273 niños prematuramente nacidos. Se han probado los niños entre 9 y 15 años, y 16.11 % han tenido »I. K.» debajo de 85. Los niños que después del parto han tenido

hemorragia cerebral, y que constituyen el 6.59 %, han tenido las mayores dificultades en la escuela y han tenido la menor cantidad de »I. K.». En todo el material reunido estos niños han empezado a andar y hablar más tarde que los niños de un grupo de control no escogido, y han mostrado peor desarrollo psíquico que los niños normales. Si no se toman en consideración los niños que han tenido hemorragias cerebrales o ataques de cianosis o los niños cuyos padres han sido imbéciles, se encuentra que se han desarrollado como niños normales. La mitad de los que han tenido hemorragias cerebrales ha tenido, en la edad escolar, paresias espásticas. Aproximadamente 50 % de los niños del material reunido ha tenido perturbaciones nerviosas, en comparación con aproximadamente el 30 % de un grupo de control no escogido. Los niños que han tenido ataques de cianosis se han portado como los que han tenido hemorragias cerebrales. Si no se toman en consideración estos casos, se encuentra que los niños prematuramente nacidos se desarrollan como los niños corrientes, aunque tienen perturbaciones nerviosas en mayor grado.

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Condition alimentaire chez les écoliers d'écoles primaires de Helsinki examinée d'après la méthode d'Oeder

Par

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Dans leurs estimations des conditions alimentaires des écoliers les médecins scolaires se sont servis depuis longtemps et se servent encore d'estimations faites à vue d'œil. Sur la base d'une impression générale, faite par l'écolier on a déduit le degré de la condition alimentaire dans de grandes lignes comme p. ex. bonne, moyenne ou mauvaise. Mais une estimation pareille est naturellement subjective et prête facilement à l'erreur.

Pourtant, l'estimation de la condition alimentaire de l'enfant peut souvent avoir une grande importance. Par conséquent, on s'est efforcé de trouver quelque méthode simple et facile à employer, p. ex. dans la sphère d'activité d'un médecin scolaire, ou en suivant le progrès de l'état alimentaire des enfants tuberculeux. Comme méthode de ce genre on a exposé *la mensuration de l'épaisseur du pannicule adipeux.* On y est parvenu, puisque le pannicule adipeux et l'état d'alimentation marchent en général du même pas, donc en estimant le pannicule adipeux, il est possible de déduire aussi les variations de la condition alimentaire. Le pannicule adipeux peut être précisé en chiffres *à l'aide d'une mensuration, par un instrument de mesure convenable, d'un pli de la peau élevé en quelque endroi convenu, le plus souvent au ventre à côté du nombril.* OEDER (1910) fut le premier à faire ainsi chez les adultes, en tâchant de développer une méthode d'examen scientifique et utilisable.

Cette méthode d'examen proposée par OEDER fut aussi appliquée aux enfants. NEUMANN (1912) fut le premier à l'utiliser

pour une estimation de la condition alimentaire, en examinant les internes d'un asile d'enfants, à Berlin, âgés de 4—17 ans avant et après le traitement, et de plus, quelques enfants de familles prospères. Il mesura alors l'épaisseur d'un pli de peau au ventre à côté du nombril moyennant un compas courbé à pointes munies de petits boutons métalliques. Au surplus des moyennes obtenues pour garçons et fillettes dans les groupes d'âge différents, NEUMANN constata alors qu'en mesurant l'épaisseur d'un pli de peau élevé on peut, d'une façon commode et avec une exactitude suffisante, estimer en chiffres l'amassement adipeux et par ce moyen, l'état alimentaire. L'épaisseur du pannicule adipeux des enfants appartenant aux familles prospères dépasse ordinairement la moyenne. NEUMANN est d'avis qu'en prenant en même temps égard à la taille et au poids on obtient une netteté encore plus grande, si l'amassement adipeux est relatif à la croissance; l'addition de la dimension du pannicule adipeux aux deux premiers nombres complète de façon essentielle la caractérisation de l'état alimentaire de l'enfant.

Plus tard plusieurs autres observateurs ont utilisé cette méthode pour estimer l'état alimentaire aux âges différents, à savoir BATKIN (1915) à Zurich, PEISER (1921) à Berlin, KUNTZE (1921) à Leipzig, KÄDING (1922) à Bonn et HILLE (1923) à Greifswald. Ils en ont fait usage en examinant les enfants bien portants ainsi que des enfants atteints de maladies différentes, en s'efforçant en même temps de perfectionner la méthode et son utilité.

Sans faire de rapports détaillés sur ces recherches, on se propose seulement ici d'attirer l'attention sur les investigations remarquables conduites dans cette sphère à Vienne par KORNFELD et SCHÜLLER (1930). A l'aide d'un pousse-compas métallique ils ont mesuré l'épaisseur du pannicule adipeux à 3 endroits différents du corps, c. à. d. sous la peau de la poitrine au-dessous de la moitié latérale de la clavicule, au-dessous la peau du ventre, d'un à deux doigts à côté du nombril, et sous la peau dorsale entre les omoplates. Pour ces examens on s'est servi d'un grand nombre d'enfants d'âges différents, à savoir d'enfants nouveau-nés jusqu'à ceux de $14\,^1/_2$ ans. Pour déterminer la moyenne on n'a choisi que les enfants dont la taille et le poids approchaient la moyenne.

Le choix se faisait ainsi que la taille et le poids de chaque enfant furent évalues selon des tables individuelles tout spécialement composées. Les enfants trop grands ou trop petits, trop lourds ou trop légers furent donc exclus de l'évaluation définitive des résultats de la mensuration. En ligne de démarcation, une déviation des valeurs moyennes contrôlées de 10 % pour le poids et de 5 % pour la taille correspondait au principe de division des groupes différents adopté comme base pour ces tables. KORNFELD et SCHÜLLER avaient eux aussi tâché de composer des groupes différents d'estimation du pannicule adipeux, auxquels on pourrait comparer les résultats individuels. De cette manière on peut obtenir une idée du développement du pannicule adipeux chez chaque individu ainsi qu'estimer la part de la graisse par rapport au poids individuel du corps.

Si nous ne tenons pas compte des propres valeurs numériques, les résultats de KORNFELD et SCHÜLLER démontrent qu'il y a, dans la moyenne de la peau de la poitrine, du ventre et du dos chez les garçons, d'abord une diminution évidente à l'âge pré-scolaire et au début de l'âge scolaire, puis, une lente augmentation à l'âge scolaire plus avancé. Chez les fillettes on constate une diminution moins évidente et transitaire dans la peau dorsale au commencement de l'âge scolaire, et dans la peau de la poitrine vers la fin de l'âge pré-scolaire. Sous la peau du ventre, d'autre part, il semble qu'il y ait une croissance continuelle du pannicule adipeux dès l'âge pré-scolaire. Le renforcement de l'épaisseur de la peau à l'âge scolaire plus avancé est encore plus marquant chez les fillettes que chez les garçons dans tous les trois endroits examinés. La différenciation caractéristique sexuelle est surtout évidente en ce que la peau du ventre s'épaissit fortement, et elle est de plus très visible sous la peau de la poitrine et le moins visible sous la peau dorsale.

Les tables de groupes différents d'épaisseur de la peau composées selon ces recherches, ont été employées ensuite avec succès par KORNFELD et SCHÜLLER dans leurs examens des rapports de l'accroissement du pannicule adipeux durant la cure de plein air des enfants chez lesquels on avait constaté une tuberculose inactive.

En me servant exactement de la même méthode que KORNFELD et SCHÜLLER j'ai fait, moi aussi (1934, 1939) plusieurs examens concernant l'utilisation du pannicule adipeux comme mesure de la condition alimentaire. Ces examens ont été faits aux écoles primaires finnoises de l'arrondissement du Nord de la ville de Helsinki, aux temps normaux avant la guerre. En guise de matière d'étude je me suis servi d'écoliers âgés de 6 $^1/_2$—13 $^1/_2$ ans, autant ceux qui possédaient un état alimentaire normal, que d'enfants plus maigres ou plus robustes qu'à l'ordinaire. De cette quantité assez grande examinée je n'ai choisi pour étude finale que des cas dont les valeurs de stature et de poids approchent à peu près les groupes de valeurs moyennes. J'ai fait le choix de la même manière que les savants viennois sus-nommés, à l'aide de tables spéciales que j'ai dû préparer d'avance tout exprès pour ces recherches. Grâce à un tel choix il ne resta pour l'étude finale que les mensurations du pli de la peau qui avaient été faites chez 587 garçons et 653 filles, donc au total 1 240 écoliers d'écoles primaires. De plus, j'ai cherché à établir, selon la méthode de KORNFELD et SCHÜLLER, des tables d'estimation afin de pouvoir préciser moyennant une comparaison à celles-ci la valeur de l'épaisseur de la peau dans chaque cas individuel dans les groupes d'âge différents, et d'arriver par là à une évaluation de l'état alimentaire de l'individu en question. Sans une telle base de comparaison il me semble qu'on ne peut pas utiliser les valeurs individuelles de l'épaisseur du pannicule adipeux pour une estimation profitable de la condition alimentaire (Table 1).

Ces recherches faites par moi démontrent que la *peau des fillettes était partout un peu plus épaisse que celle des garçons dans tous les endroits examinés, et que le pannicule adipeux était en général le mieux développé au ventre.* De plus, on a pu constater que le pannicule adipeux de la peau du ventre reste sans changements chez garçons et filles les premières années à l'école, mais dès l'âge de 10 ans il commence à augmenter lentement chez les garçons et s'agrandit d'une année à l'autre (Table 1). Chez les fillettes, par contre, cet agrandissement du pannicule adipeux au ventre commence déjà à l'âge de 9 ans et se développe d'année en année en grandissant toujours. La moyenne de l'épaisseur du

Table 1.

Valeur moyenne de l'épaisseur du pannicule adipeux au ventre chez garçons et fillettes de taille et poids moyens.

Age ans[1]	Garçons		Fillettes		Garçons	Fillettes
	Nombre d'enfants examinés	Moyenne mm	Nombre d'enfants examinés	Moyenne mm	Valeurs moyennes arrondies mm	
7	45	7,7	36	8,8	7,5	9,0
8	94	7,9	85	9,1	8,0	9,0
9	101	7,8	103	9,5	8,0	9,5
10	74	8,3	114	11,5	8,5	11,5
11	79	8,8	122	12,0	9,0	12,0
12	84	9,3	105	14,5	9,5	14,5
13	86	10,5	70	15,8	10,5	16,0
Au total	563		635			

pli de la peau était selon mes recherches chez les garçons de p. ex. 9 ans de 8,0 mm et chez les fillettes de 9,5 mm; à l'âge de 13 ans 10,0 mm chez les garçons et 16,0 mm chez les fillettes. Cette augmentation considérable du pannicule adipeux chez les filles est naturellement un agrandissement général du pannicule adipeux causé par la pré-puberté.

L'épaisseur du pannicule adipeux n'a pas subi de variations semblables sous la peau de la poitrine, ni sous la peau dorsale. Les moyennes restaient à peu près les mêmes pour les groupes d'âge plus jeunes, et une augmentation lente ne pouvait être constatée que dès la 10-me année. Chez les filles cela était plus évident dans la peau de la poitrine.

Les résultats que j'ai obtenus correspondent d'une manière étonnante à ceux constatés chez les enfants de Vienne. Il n'y a guère de divergence dans les moyennes d'épaisseur du pannicule adipeux au ventre et au dos. Par contre, les moyennes représentant l'épaisseur de la peau de la poitrine sont plus grandes chez les enfants viennois, garçons et filles, que chez les enfants de Helsinki. Cette différence peut avoir son explication dans une application de la mensuration aux places différentes.

[1] 7 ans = 6 $^1/_2$—7 $^1/_2$ ans; 8 ans = 7 $^1/_2$—8 $^1/_2$ ans etc.

Mes nouvelles recherches

J'avais déjà essayé plus tôt d'utiliser en pratique les tables d'estimation sus-dites représentant les degrés différents de l'épaisseur du pannicule adipeux des groupes d'âge divers, lors de mes examens des écoliers avec poids dit inférieur au poids normal. Cela se faisait à propos d'autres recherches nombreuses concernant l'état physique de tels enfants. Selon mes expériences ces tables se sont montrées utilisables. Grâce à mes connaissances acquises de cette manière je suis arrivé à la conclusion que la méthode expliquée ici *d'une mensuration d'un pli de peau élevé peut être adaptée avec succès entre autres aux examens de la condition alimentaire des écoliers*, surtout si l'on se sert, *en base de comparaison, des tables d'estimation* présentées ci-dessus.

Afin de pouvoir me servir de cette méthode d'examen de l'état alimentaire dans une plus grande extension, j'ai décidé d'examiner de cette manière *tous les écoliers des écoles primaires finnoises de l'arrondissement du Nord de Helsinki* et de plus, *à titre de comparaison, les écoliers d'une école de l'arrondissement du Sud.* Pour la mensuration de l'épaisseur du pli de la peau je me suis servi, comme dans mes recherches antérieures, d'un petit pousse-compas métallique donnant les valeurs exactes en millimètres, l'élève étant debout. J'ai soulevé le pli de la peau dans le sens de la longueur, cette fois-ci la peau du ventre un peu à droite du nombril. Lors de la mensuration, j'ai contrôlé toujours que le pli de la peau ne soit pas serré entre les pointes de l'instrument, mais que ces pointes touchent juste les deux surfaces du pli de la peau de tout son long.

J'ai fait ces examens de l'état alimentaire au cours des années 1938—39, donc avant nos deux dernières guerres, quand l'état général alimentaire dans notre pays était encore bon et normal. J'ai fait ces examens dans les écoles qui se trouvaient dans mon district de médecin scolaire, à savoir les écoles primaires d'Alexis Kivi, Kallio, Vallila, Käpylä et Toukola, et de plus, à l'école primaire de Töölö. Mes recherches comprenaient tous les écoliers âgés de $6\,^1/_2$—$13\,^1/_2$ ans. Je n'ai pas pu examiner de cette façon les écoliers plus âgés, mes tables d'évaluation ne donnant que

les âges mentionnés. Le nombre total d'écoliers examinés fut de 6 005, dont 3 027 garçons et 2 978 fillettes. Le nombre d'écoliers examinés se répartit entre les écoles différentes comme suit:

Ecole	Garçons	Fillettes	Au total
Ecole d'A. Kivi	963	980	1 943
» de Kallio	753	702	1 455
» » Vallila	433	486	919
» » Käpylä	305	275	580
» » Toukola	130	120	250
» » Töölö	443	415	858
Au total.....	3 027	2 978	6 005

J'ai estimé l'état alimentaire des élèves de chaque école par groupe d'âge, séparément pour garçons et fillettes. Comme la publication de ces tables tout entières prendrait trop de place, j'ai essayé de les ramener à une seule table, démontrant les résultats sous une forme concentrée aussi bien que possible.

La table 2 nous présente un sommaire des résultats obtenus de la mensuration du pli de la peau du ventre de 6 005 écoliers. Il en ressort en premier lieu que l'épaisseur du pannicule adipeux sous la peau du ventre avait une valeur moyenne chez 35 % de tous les écoliers, autant garçons que filles, des écoles primaires de l'arrondissement du Nord, autrement dit, *leur condition alimentaire était donc bonne en moyenne.* En second lieu, nous voyons que le pannicule adipeux au ventre était plus mince que l'épaisseur moyenne chez 7,6 %, mais plus épais que la moyenne et même très épais, chez 57,6 % de tous les garçons et fillettes ensemble. En d'autres termes, *à peine un huitième* de tous les écoliers de l'arrondissement du Nord *avaient un état alimentaire inférieur à la moyenne et même mauvais, tandis que plus de la moitié d'entre eux avaient un état alimentaire surpassant la moyenne et même très bon.*

Si d'autre part nous examinons séparement les valeurs de la mensuration de la peau du ventre chez garçons et filles, nous voyons qu'environ 40 % du nombre total des garçons et environ 29 % du nombre total des filles avaient *un bon état alimentaire* moyen. Nous voyons de plus que 8 % des garçons et 7 % des filles

Table 2.

Distribution en groupes différents exprimée en % de l'épaisseur du pannicule adipeux au ventre chez garçons et fillettes.

	Mince %	Au dessous d'épaisseur moyenne %	Epaisseur moyenne %	Dépassant épaisseur moyenne %	Epais %	Très épais %
Ecoles de l'arrondissement du Nord						
Garçons.....	2,2	5,9	*40,2*	11,4	21,2	19,1
		8,1			*51,7*	
Fillettes	1,4	5,8	*29,3*	16,2	18,8	28,5
		7,2			*63,5*	
Garçons et fillettes	1,8	5,8	*34,8*	13,8	20,0	23,8
		7,6			*57,6*	
Ecole de Tõõlõ						
Garçons.....	0,7	3,2	*30,0*	13,3	20,7	32,1
		3,9			*66,1*	
Fillettes	1,9	4,4	*20,2*	14,2	20,5	38,8
		6,3			*73,5*	
Garçons et fillettes	1,3	3,8	*25,1*	13,7	20,6	35,5
		5,1			*69,8*	

étaient *au-dessous* et 51,7 % des garçons et 63,5 % des filles *au dessus de la condition alimentaire moyenne*. Par conséquent, *la condition alimentaire des filles était en général évidemment meilleure que celle des garçons*. Aussi, il y avait parmi les garçons un total de 2,2 % dont le pannicule adipeux au ventre était mince, c. à. d. *la condition alimentaire mauvaise*. Pour les fillettes, la valeur correspondante n'était que de 1,4 %. D'autre part, il y avait de même un pannicule adipeux très épais, donc *une condition alimentaire extrèmement bonne*, chez 19 % de tous les garçons, donc presque chez chaque cinquième. Tandis qu'il y avait beaucoup plus d'écolières avec un tel état alimentaire extrèmement bon, à savoir un total de 28,5 % ou moins que chez chaque troisième.

Afin de rendre les concepts plus clairs il importe de mentionner dans ces rapports que les valeurs de mensuration les plus faibles de ces recherches furent telles que 3,5—4,5 mm chez les garçons et 3,5—6,0 mm chez les filles, selon les groupes d'âge. La valeur la plus basse de l'épaisseur de la peau au ventre rencontrée par moi dans ces recherches fut de 3,5 mm chez les garçons et de même, 4,5 mm chez les fillettes. Une si petite épaisseur de la peau du ventre fut trouvée par moi chez deux garçons et une fillette. Il se trouvait pourtant chez les garçons des valeurs aussi faibles que 4 et 5 mm, ainsi que 5 et 6 mm chez quelque fillette. Si nous nous efforçons d'imaginer la peau du ventre de quelque enfant de 7 ans, dont l'épaisseur du double pli de la peau n'est que de 3,5 ou 4 mm au total, nous pouvons concevoir facilement, qu'il ne peut guère être question d'un pannicule adipeux quelconque. D'autre part, je peux dire que de telles valeurs comme 38—44 mm d'épaisseur du pli de la peau du ventre représentent des valeurs appartenant à un groupe très haut. J'en ai très souvent trouvé de telles chez les garçons, et surtout chez les filles. La plus grande valeur de l'épaisseur de la peau du ventre et par conséquent du pannicule adipeux que j'ai trouvée chez les garçons était de 45 mm, et les valeurs de mensuration correspondantes chez les filles étaient de 46 et 48 mm. Une exacte mensuration de telles valeurs est déjà assez difficile.

Donc, selon cette méthode de recherches *l'état alimentaire des écoliers des écoles primaires de l'arrondissement du Nord de Helsinki fut à ce temps-là en général meilleur que la moyenne, même extrèmement bon, chez une part considérable, assez bon et seulement chez une partie relativement petite, assez mauvais ou directement mauvais.*

Il est intéressant d'établir un parallèle entre ces résultats et ceux appartenant au district scolaire du Sud, et d'examiner, à titre de comparaison, les résultats que j'ai obtenus chez les écoliers de l'école primaire de Töölö. Ces résultats ressortent eux aussi de la table 2. Nous y voyons que *les valeurs du pannicule adipeux au ventre étaient partout plus avantageuses que celles des écoliers des écoles primaires du district du Nord.* Cela se voit, en premier lieu, dans les pourcentages de ces écoliers — garçons et filles — dont le pannicule adipeux au ventre était d'une épaisseur moyenne, ou autrement dit, l'état alimentaire assez bon, ces pourcentages étant beaucoup plus faibles que dans les écoles de l'arrondissement du Nord. En effet, il n'y avait au total que 25 %, à savoir un quart de tous les garçons et fillettes réunis à l'école de Töölö, tandis que

la valeur correspondante se trouvait chez 35 % à l'arrondissement du Nord, donc environ 10 % de plus. En second lieu, il est digne d'observation que *5 % seulement* des écoliers de la dite école avaient un pannicule adipeux plus mince que la moyenne, autrement dit, *un état alimentaire assez mauvais ou mauvais.* Nous voyons de plus qu'il était en général plus épais que la moyenne et même très épais, en autres termes, *une condition alimentaire bonne ou très bonne chez 70 %* de tous les garçons et fillettes ensemble (valeur correspondante dans l'arrondissement du Nord env. 58 %). En troisième lieu, nous pouvons constater ce qui suit: les valeurs de la mensuration du pannicule adipeux obtenues à l'école de Töölö, en mesurant garçons et filles séparément, étaient pour les groupes inférieurs à la moyenne, c'est-à-dire 3,9 % respectivement 6,3 %, nettement plus petites, et pour les groupes supérieurs à la moyenne, à savoir 66,1 % respectivement 73,5 %, considérablement plus grandes que les valeurs correspondantes chez les écoliers de l'arrondissement du Nord. C'est à dire, *les écoliers de l'école de Töölö étaient, à l'égard de leur état alimentaire, dans une meilleure condition que les enfants des écoles primaires de l'arrondissement du Nord.* Donc en général la différence entre les valeurs numériques representant les épaisseurs du pannicule adipeux dépassant la moyenne et très épais, était chez les garçons ainsi que chez les filles à de l'école primaire de Töölö de 10 % plus grande, de même la différence des valeurs de peau très épaisse était plus grande de 10,3—13 % qu'à l'arrondissement du Nord. Parmi tous les écoliers de l'école de Töölö environ *12 % avaient un bon état alimentaire, de même env. 12 % de plus que dans les écoles de l'arrondissement du Nord.* Donc les premières valeurs correspondant entre elles étaient 69,8 et 57,6 %, et les dernières 35,5 et 23,8 %. Je reviendrai bientôt sur la question d'où cette différence provient éventuellement.

Il n'est pas nécessaire d'examiner ici en détail quels furent les résultats de la mensuration du pannicule adipeux au ventre, obtenus dans les écoles différentes.

Mes recherches, comme je l'ai déjà décrit en détail ci-dessus, ont prouvé entre autres choses, que les écoliers de l'école primaire de Töölö étaient à l'égard de leur état alimentaire dans des con-

ditions évidemment meilleures que les élèves des écoles primaires de l'arrondissement du Nord de Helsinki. Certes il y avait et il y a encore des élèves à l'école de Töölö dans de mauvaises conditions alimentaires, mais leur nombre était petit, et il y avait beaucoup plus d'élèves ayant un bon état alimentaire qu'à l'ordinaire parmi les enfants des écoles primaires de l'arrondissement du Nord. Ce phénomène s'explique si nous examinons *les conditions de logement et de famille des élèves de l'école de Töölö.*

Il est connu depuis longtemps que les lycéens autant en Finlande qu'ailleurs sont en général plus grands et plus lourds que les enfants des écoles primaires du même âge. On a essayé d'expliquer ce phénomène comme étant dû à la situation sociale et à la prospérité des parents. Cette explication est bien fondée dans les grandes lignes, quoiqu'il y ait des exceptions individuelles dans les deux sens. L'état mauvais d'un enfant de famille aisée est dû evidemment aux facteurs internes réglant la croissance, où la prospérité de la famille ne peut pas toujours apporter de changements. Mais en général, la situation sociale de la famille a, comme j'ai déjà dit, une influence évidente sur l'état physique de la jeunesse grandissante. Ce fait est clairement révélé par mes recherches dont il est question ici.

Au surplus du travail exposé ci-dessus, j'ai aussi fait des examens dont l'objet fut la situation sociale et les conditions de logement des élèves de l'école de Töölö ainsi que de ceux des écoles primaires de l'arrondissement du Nord de Helsinki. En effet, on savait déjà que ces conditions n'étaient nullement les mêmes dans le district de Töölö que dans l'arrondissement du Nord. A l'aide de ces examens j'ai essayé d'exposer cette difference en chiffres.

Bref, j'ai pu constater moyennant ces examens que *les conditions de logement des enfants de l'école de Töölö étaient évidemment et à tous les égards plus avantageuses que celles des élèves des écoles primaires de l'arrondissement du Nord*, à l'exception de la banlieue de Käpylä, où elles se rapprochaient des conditions premièrement nommées. Cette différence dans les conditions de logement, avantageuses aux enfants à l'école de Töölö, dépend évidemment *de la situation sociale de ces familles.*

Résumé

A la suite de mes recherches antérieures et des expériences obtenues pendant les recherches en question, je suis arrivé à la conclusion que *la méthode de mensuration d'un pli de la peau élevé* peut être utilisée avec succès p. ex. pour préciser en chiffres l'état alimentaire des écoliers, surtout si l'on se sert en même temps, comme base de définition, *de tables spéciales d'estimation* se rattachant à cette méthode d'examen.

Summary

On the basis of my earlier research and the experience gained in connection therewith, I have come to the conclusion that measurement of a raised fold of skin provides an effective means of for example determining numerically the state of nourishment of school children. The method is particularly successful if combined with special evaluation tables affording a basis of definition.

Zusammenfassung

Auf Grund meiner früheren Forschungen und der dabei gemachten Erfahrungen kam ich zu dem Ergebnis, dass die Methode, eine abgehobene Hautfalte zu messen, mit Erfolg angewendet werden kann, um z. B. den Ernährungszustand der Schulkinder in Ziffern festzulegen, besonders wenn man dabei als Bestimmungsgrundlage spezielle, sich auf diese Untersuchungsmethode beziehende Werttabellen benützt.

Resumen

Partiendo de mis investigaciones anteriores y de las experiencias acumuladas durante las mismas, he llegado a la conclusión de que el método de medición de un pliegue elevado de la piel puede ser utilizado ventajosamente, por ejemplo para precisar en cifras el estado alimenticio de los escolares, sobre todo si al mismo tiempo se usan, como base de definición, cuadros especiales de estimación sujetos a este método.

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(FROM THE EPIDEMIC DEPARTMENT OF ULLEVÅL HOSPITAL — THE MUNICIPAL HOSPITAL IN OSLO — SENIOR PHYSICIAN: P. M. HOLST, M. D.)

Complications of Scarlet Fever in Oslo During the Period 1890—1947

By

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As the epidemics of scarlet fever have apparently changed character during the last few decades, an investigation has been undertaken in order statistically to trace this change by registering the mortality, relapses, and total complications in several groups of years of patients admitted to the Epidemic Department of Ullevål Hospital during the greater epidemics between 1880—1948.

From previous publications (1, 2), it is evident that when scarlet fever first occurred in the North, it took a severe form which it retained until the end of the nineteenth century, while later epidemics reverted to a milder type. In the latter part of the nineteenth century, however, some cases of scarlet fever took the so-called virulent form with gangrenous angina.

Salomonsen (2) describes the first epidemic in Denmark in 1759 and states that the disease soon took a severe form which »very nearly tore away all those affected». The mortality in Copenhagen amounted to 1.64 per cent of the population during the epidemics of the nineteenth century, and in 1787 scarlet fever spread to Norway.

From Sweden Lichtenstein (3) states that since 1871—1880 the mortality has decreased considerably.

In Helsingfors the mortality in the period 1880—1890 was 14—30 per cent of those affected (4), and during the epidemic of 1906—14 the mortality was still 3.8—15 per cent.

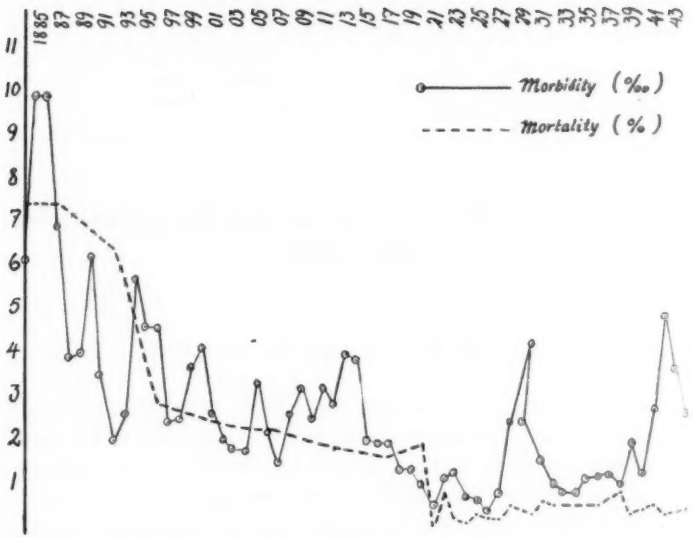

Fig. 1. Morbidity and mortality rates for scarlet fever in Norwegian cities (1884—1944).

As a parallel to the material from Ullevål Hospital, some figures will be given here on the complication frequency in Sweden and Finland, since these figures seem generally to lie above the figures of this material.

From the 1934 epidemic in Stockholm the following figures (5) are given: otitis 30 per cent — 10 per cent of whom underwent mastoid operations, — nephritis 5 per cent, and relapses 14 per cent.

Relapses are stated to have increased from 1 per cent in the last part of the nineteenth century to 10 per cent of all cases in 1929. After penicillin treatment was introduced, the following figures were given for those treated and not treated, respectively (6): cervical adenitis 2.2 (30.1), sinusitis 0.4 (1.8), otitis 0.0 (10.5), nephritis 0.4 (0.9) and relapses 0.4 (8.5).

From the epidemic in Helsingfors in 1906—1914 we have obtained the following figures: adenitis 1.7—7.6 per cent, rhi-

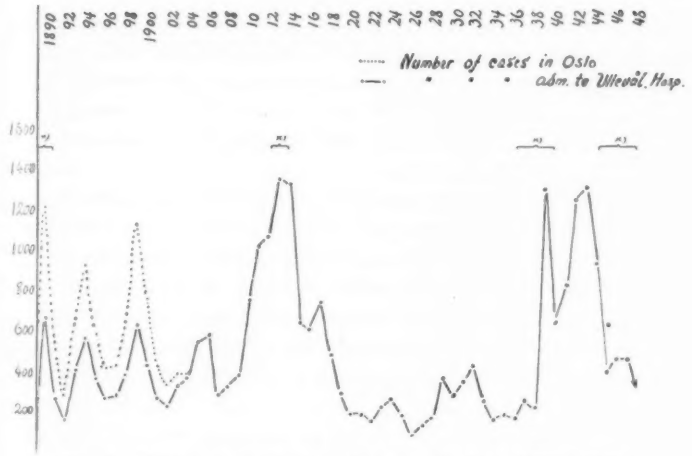

Fig. 2. Number of cases of scarlet fever in Oslo (1890—1947).
×) The material for this investigation.

nitis 0.0—2.4 per cent, complications from respir. org. 0.7—7.7 per cent, otitis 11.7—21.7 per cent, kidney compl. 9.1—27.7 per cent, and relapses 1.0 per cent. The frequency of complications was highest at the beginning and end of the epidemic (4).

The figures from Denmark are about the same as in this material. The frequency of complications after penicillin treatment and careful isolation is practically nil (8). In later years relapses have occurred in 2—3 per cent (1—10 per cent) of all cases (7).

As to the epidemic in Norway in 1890, it is stated in a report by the Christiania Health Commission that the epidemic declined in 1891—1892 but increased again in 1893, with a mortality of 7 per cent of all cases, »a favourable death-rate». The mortality in 1890 was 7.8 per cent and in 1887 as high as 12.8 per cent. Later reports (9), however, show a rapidly declining mortality during the following years. This appears plainly in Fig. 1, which gives morbidity and mortality curves for the cities since 1884, the mortality in per mille of the population, and

the mortality in per cent of those affected. Fig. 2 records all cases in Oslo and those admitted to Ullevål Hospital, Epid Depart. In this Figure there are 2 curves for the period 1890—1903, as in this period only 60 per cent of all cases were admitted to the hospital, while after 1903 practically 100 per cent were admitted.

According to these figures there was no great epidemic before 1913 except for an increase in 1894 and 1899. After 1913 there was no epidemic (with the exception of small epidemics in the period 1929—1932) till the great epidemic of 1939—1947. This last epidemic was already underway in 1937. The fall of the curve in 1940 is artificial and due to the outbreak of the war as a great number of the patients in the Epidemic Department were discharged 9/4 1940.

The isolation period advocated in Oslo was formerly 6 weeks, except during a relatively short time, which when it was 4 weeks does not concern this material. Since the introduction of penicillin treatment the isolation period has been reduced to 9 days with treatment the first 6, but further isolation is recommended if there are complications. All the patients discharged the ninth day must meet for a check-up 1—2 and 3 weeks, respectively, after discharge from the hospital.

During recent years all the patients have upon admission to the hospital been placed in separate rooms for observation during the first 24 hours. On the second day cases without complications are moved to small wards of 2—3 beds and later on to larger hospital wards where they are out of bed. All cases with complications are isolated if possible, but the lack of isolation units makes it impossible to make this policy a general rule.

During the years 1937—1938—1939 some cases, especially the more severe ones, were treated with convalescent serum without any striking effect (10). In 1939 some cases were treated with prontocil, but according to the records and former publications without special effect. In Oct.—Nov.—Dec. 1939 150 cases were treated with sulfapyridin (mentioned later on).

By order of the Department of Health a few patients in 1946 and all the patients in 1947 were treated with penicillin for 6

days, with the exception that in Nov.—Dec. 1947 the milder cases were treated only 3—4 days but isolated for 9 days like the others. The dose of penicillin was 10—20 000 units every 4 hours.

The material for this investigation is derived from the epidemics of 1890, 1913, and 1939—1947, the records of all patients during the years 1880, 1913, 1937, 1938, 1939, 1945, 1946 and 1947 having been examined (a total of 5 100 cases).

From the 3 epidemics the years 1890, 1913, and 1939 were selected. As these 3 years were from corresponding periods within the respective epidemics and in them the admissions reached a peak, it was felt that they would be best suited to comparison of mortality and complication-frequency, according to the known fluctuations within the course of single epidemics (4—11). Bjørksten states with regard to the epidemic of scarlet fever in Helsingfors 1906—1914 that the mortality was highest during the first part of the epidemic and that the frequency of most of the complications was highest at the beginning and the end of the epidemic (intestines and urinary and respiratory organs). Otitis occurred during the whole epidemic but with a slight predominance in the middle corresponding to the maximum morbidity.

The years 1937, 1938 and 1945, 1946, 1947 constitute the beginning and end of the last epidemic and form the bases of the estimation of the results of the treatment introduced in the latter part of the epidemic.

The present material has yielded the following figures concerning the occurrence of scarlet fever.

With regard to the time of year, most of the cases occurred in Sept.—Oct.—Nov. (Table 7, see below).

With regard to the sexes, females predominated with 53.8 per cent, but there is a corresponding majority in the population of Oslo (1946: 55.25 per cent).

The relative frequency of scarlet fever in the different age groups was as follows: Under 1 year: 38 cases (0.7 per cent); 1—10 years: 3 039 cases (59.6 per cent); 10—20 years: 1 406

cases (27.6 per cent); over 20 years: 617 cases (12 per cent). Out of the 38 cases under 1 year, 20 date from the year 1890. Of these 16 were under the age of 11 months and of these in turn 8 under the age of 9 months. Among the remaining 18 cases from the later years, 11 cases were under the age of 11 months and of these in turn 8 under the age of 9 months.

Scarlet fever usually does not occur under the age of 6 months (12). In this material there are 2 cases under the age of 6 months, both from the year 1890 and 5 months old, but in both cases the diagnosis was stated as doubtful. One of the children was admitted to the hospital with its mother, who suffered from scarlet fever. Under the age of 11 months scarlet fever is uncommon. During the course of the last 6 years covered by this material (from 1937) only 4 cases occurred, or 1.3 per cent. With regard to the particular day during the course of the disease on which the patient was admitted to the hospital we have the following figures for the years 1945, 1946, 1947: Admitted on the first and second days of the disease: 26 per cent; third and fourth days: 48 per cent; fifth and sixth days: 15 per cent; later: 11 per cent.

40 of all the patients had had scarlet fever once before, or 0.8 per cent of the whole material.

The frequency of mortality, the relapses, and the frequency and distribution of the most common complications within the groups of years examined are shown in Table I. During the whole period mortality decreased at an even rate except for a small increase in 1945. In 1890 the most frequent cause of death was »angina ulcerosa», sometimes together with otitis, and in addition pneumonia and paralyses of the heart are noted. Death occurred most frequently during the 2nd and 3rd weeks. In 1913 also »angina ulcerosa» was given as the cause of death in several cases; other causes were peritonsillar abscess, lymph nodes with suppuration, pneumonia, and uremia. In 1945 there were 4 cases which ended in death; these included a narcosis death during ethmoidal resection and deaths due to pneumonia, endocarditis and mastoiditis in a case of celiac disease. In 1946 there were 2 deaths occasioned by pneumonia and nephritis.

Table I.

Percentage of cases with the most common complications.

Year	Cases	Mortal.	Relapse	Adenit.	Angina	Rhinit.	Otit	Mast	Sinusit.	Bronchit	Pneumoni	Myopath	Myocard	Nefrit	Rheum. scarl.
1890	668	7.8	—	4.5	3.7	0.6	13.3	—	—	0.2	0.3	—	—	7.2	5.5
1913	1 338	1.6	1.9	8.2	4.2	0.9	9.3	0.8	0.1	1.1	0.2	0.1	0.1	2.2	3.7
1937	259	0.8	5.8	28.5	0.8	1.2	11.5	4.2	0.4	0.4	1.2	5.4	1.9	3.5	0.8
1938	208	0.5	3.3	25.0	5.2	0.5	15.2	6.2	1.0	1.0	0.5	2.4	1.0	1.4	1.9
1939	1 298	—	0.8	23.9	6.9	1.5	6.1	0.8	0.2	—	0.2	0.4	0.2	2.6	1.1
1945	400	1.0	1.0	28.5	2.5	3.5	16.5	7.0	12.0	1.3	2.5	0.3	—	2.0	11.5
1946 ÷ pen...	338	0.6	0.6	28.8	1.5	2.6	16.8	10.3	8.8	—	1.5	0.9	—	1.5	13.2
+ pen...	128	—	0.7	20.3	5.4	3.8	7.7	2.3	3.8	—	—	0.7	—	—	12.3
1947	463	—	0.4	14.3	1.7	5.7	4.7	0.4	4.3	0.4	0.6	—	—	0.2	3.6
1947 ÷ pr. kpl.	420	—	0.4	13.3	1.7	2.6	0.7	—	2.4	0.2	0.2	—	—	—	2.9

pen = penicillin. pr. kpl. = primary complications: i. e. complic. which occurred before admission or on the first day in the hospital.

Table II.

Percentage of the most common complications among cases treated with sulfapyridin and those not treated.

Oct.—Nov.—Dec. 1939	Cases	Relapse	Adenit.	Angina	Rhinit.	Otit	Mast	Sinusit.	Bronchit	Pneumoni	Myopath	Myocard	Nefrit	Rheum. scarl.
+ sulfapyridin	150	0.0	13.3	5.3	2.7	5.3	0.7	—	—	—	0.7	—	0.7	—
÷ sulfapyridin	550	0.9	26.0	12.0	2.2	6.9	0.5	—	—	—	0.4	—	4.4	2.0

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Table III.

Percentage of complications according to age.

Age	Cases	Per cent	Relapse	Adenit.	Angina	Rhinit.	Otit	Mast	Sinusit.	Bronchit	Pneumoni	Myopath	Myocard	Nefrit	Rheum. scarl.
1890															
< 1	20	3.0	—	—	—	—	(50)	—	—	—	—	—	—	—	—
1–10	545	81.6	—	4.6	3.5	0.6	14.9	—	—	0.2	0.4	—	—	7.7	4.5
10–20	84	12.6	—	6.0	7.2	—	4.8	—	—	—	—	—	—	5.9	10.7
> 20	19	2.8	—	—	—	—	—	—	—	—	—	—	—	5.3	21.0
1913															
< 1	11	0.8	(18)	(9)	—	—	(45)	(9)	—	(9)	(9)	—	—	—	—
1–10	854	63.8	2.1	8.4	4.2	1.3	11.4	1.0	—	0.9	0.4	0.1	0.1	2.6	1.8
10–20	410	30.7	1.2	8.8	4.4	—	4.9	0.2	0.2	—	—	—	—	1.7	6.8
> 20	63	4.7	1.6	1.6	3.2	1.6	3.2	—	—	—	—	1.6	—	—	7.9
1937															
< 1	0														
1–10	141	54.4	9.2	39.0	0.7	0.7	19.0	6.3	0.7	0.7	2.1	4.9	2.1	2.8	—
10–20	74	28.6	2.7	22.4	—	1.4	2.7	2.7	—	—	—	6.8	1.4	4.1	2.7
> 20	44	17.0	—	4.5	2.3	2.3	4.5	—	—	—	—	4.5	2.3	4.5	2.3
1938															
< 1	0														
1–10	110	52.9	5.5	32.7	3.6	—	26.4	11.8		1.8	0.9	2.7	0.9	0.9	0.9
10–20	60	28.8	1.7	25.0	6.7	—	5.0	—	1.7	—	—	—	—	3.3	3.3
> 20	38	18.3	—	5.3	7.9	2.6	—	—	2.6	—	—	2.6	2.6	—	2.6
1939															
< 1	0														

10–20	60	28.8	1.7	25.9	6.7										
> 20	38	18.3	—	5.3	7.9	2.6	—	—	2.6	—	—	2.6	2.6	—	2.6
1939															
< 1	0														
1–10	671	51.7	1.2	32.0	6.6	1.5	7.7	0.9	—	—	0.1	0.5	0.3	3.1	0.4
10–20	521	40.1	0.4	15.0	6.9	1.0	4.6	0.6	0.2	—	—	0.2	—	1.9	1.0
> 20	106	8.2	—	11.3	8.5	3.8	2.8	0.9	0.9	—	—	1.9	—	1.9	5.7
1945															
< 1	4	1.0	—	—	—	—	—	—	—	—	—	—	—	—	—
1–10	159	39.8	0.6	35.2	3.1	5.6	28.9	10.1	11.9	1.3	2.6	—	—	3.1	3.7
10–20	97	24.2	2.1	34.0	3.1	2.1	11.3	2.1	13.4	1.0	2.1	—	—	2.1	6.2
> 20	140	35.0	0.7	17.8	1.4	2.1	4.3	1.4	10.7	0.7	2.8	0.7	—	0.7	24.3
1947															
< 1	3	0.7	—	—	(33)	—	—	—	—	—	—	—	—	—	—
1–10	328	70.9	0.6	19.0	2.1	5.5	6.1	0.6	3.7	0.3	0.3	—	—	0.3	0.3
10–20	62	11.3	—	3.2	—	12.9	1.6	—	9.7	—	—	—	—	—	4.8
> 20	70	15.1	—	2.9	—	1.4	1.4	—	2.9	1.4	2.9	—	—	—	18.6
1947[1]															
< 1	3	0.7	—	—	(33)	—	—	—	—	—	—	—	—	—	—
1–10	289	68.8	0.7	18.1	2.1	2.1	1.0	—	2.4	0.3	—	—	—	—	0.7
10–20	60	14.3	—	3.1	—	6.3	—	—	4.8	—	—	—	—	—	3.1
> 20	68	16.2	—	2.9	—	1.3	—	—	—	—	2.9	—	—	—	11.9

( ) the few cases in these groups give rel. too high per cent.

[1] ÷ primary complications.

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Table

Number of cases with

Treatment	Cases	Alburia	Eeg.[1]	Peritons absc.	Adenit. absc.	Stomatit.	Post sc. fev.	Impetigo	Empyema	Pericard	Endocard	Pyemia.
÷ penicil.....	4509	62	56	11	19	—	9	4	11	1	2	7
+ penicil.....	591	18	3	1	1	2	4	2	—	—	—	1

[1] Without clinical symptoms (from 1937, 2 509 cases).

The relapses have also decreased at an even rate except for the year 1890, for which no cases are mentioned in the records, and the year 1913, with only 1.9 per cent. This figure may be due to deficient observation or it may be in accordance with the corresponding observation of Lichtenstein from Sweden (13), *i.e.* that during the last century relapses have occurred only rarely, in scarcely 1 per cent of all cases, but later increased.

Where complications are concerned, attention must first be called to the fact that since 1937 all cases of adenitis have been mentioned as soon as they have given the slightest reaction of fever. Unless due regard is paid to this the figures are rather high and misleading. In most cases the adenitis was rather moderate, with periadenitis in only a very few instances. The frequency of adenitis was rather constant until the introduction of penicillin, when it decreased.

The frequency of angina and rhinitis is increasing, possibly because of more accurate observation during recent years. The same is true of sinusitis. The frequency of otitis and mastoiditis is likewise increasing except for an obvious fall in 1939 due not merely to the fact that about 10 per cent of the material was treated with sulfapyridin. Table II shows the result of the treatment. There is another increase in 1945—1946 but again a considerable decrease after the introduction of penicillin. Carditis has shown a tendency to decrease, as has nephritis except for the years 1939 and 1945. Most of the cases of nephritis have been mild (64 per cent) and by the discharge clinical signs have

IV.

rarer complications.

Polyarth.	Herpes.	Erysipl.	Pleurisy	Menin-git.	Jaundice	App. ac.	Conj.	Enceph.	Orchit.	Vaginit.	Osteomyel.	Pyarth.	Purpura fulm.
9	3	11	3	9	8	2	5	1	1	2	1	2	—
—	—	—	—	1	—	—	4	—	—	—	—	—	—

disappeared, in a few cases only after several weeks' stay in the hospital (Table V).

Transient albuminuria persisting in most cases only for a few days appears especially on the first and second days of the disease and is relatively rare as late as the third week. The frequency of albuminuria in the 8 groups of years observed was, respectively, as follows: (1890—1947): 2.7 — 0.8 — 6.2 — 1.9 — 0.9 — 0.3 — 0.0 — and 3.8 per cent There was relatively high frequency in 1947 during penicillin treatment.

Scarlatinal rheumatism has been relatively frequent during recent years, but in all cases only slight and transient symptoms occurred. Cases with real polyarthroitis have been of relatively rare occurrence and are shown in Table IV.

The frequency of complications in the 2 years 1913 and 1939, which represent the maximum morbidity during the 2 epidemics, is nearly identical.

The high frequency of complications in 1945, when the morbidity frequency had begun to fall, is striking. The frequency of relapses and complications in the different age groups is shown in Table III.

Relapses occur most frequently in the age group 1—10 years, according to a Swedish publication (13). Complications likewise occur most frequently in the age group 1—10 years, except for sinusitis, amongst others, which occurs more frequently among the higher age groups, since more of the sinuses are not sufficiently developed during infancy. Cardiac complications also occur more frequently in the higher age groups.

Table V.

Number of cases with nephritis, and with and without protein and blood in the urine upon discharge from the hospital.

Year	—90	—13	—37	—38	—39	—45	—46	—47
Mild Cases.....	29	22	6	2	22	3	3	—
Severe »	19	7	3	1	12	5	2	1

Table VI shows the occurrence of relapses and complications during the course of the disease. Relapses usually appeared within the first 4 weeks. Adenitis and rhinitis appeared in equal proportions during the course of the disease, while angina most frequently appeared during the later part of the course. Otitis occurred most frequently during the first week, but also frequently during the second and third weeks.

Mastoiditis occurred in the third and fourth weeks. Sinusitis occurred most frequently within the 2 first weeks and likewise pneumonia, while bronchitis occurred later. The cardiac complications and nephritis developed in the third and fourth weeks. Transient albuminuria occurred, as mentioned, on the first and second days. Scarlatinal rheumatism appeared nearly exclusively in the first week.

The connection of scarlet fever and its complications with the seasons appears from Table VII. Scarlet fever shows, as was mentioned before, a seasonal increase in winter and according to Schiøtz (14) maximum morbidity in Nov. In this material, however, the maximum morbidity was distributed equally among Sept., Oct., and Nov.

The year 1938 proved an exception, with its maximum in March but high frequency in Oct., while in the year 1939 scarlet fever had a great flush in July, although the maximum was reached in Nov.

Adenitis occurred equally throughout the year, while otitis and nephritis were most frequent from Febr. to June.

Electrocardiographic changes without clinical symptoms appeared in 1937 in 10.8 per cent, in 1938 in 5.7 per cent, later in

Table VI.

Percentage of compl. and relapses throughout the course of the disease (1880—1946).

Date	Adenit.	Angina	Rhinit.	Otit	Mast	Sinusit.	Bronchit	Pneumoni	Myopath	Myocard	Nefrit	Rheum. scarl.	Date	Relapse
first week.....	27	19	30	36	2	37	17	33	3	10	19	82	4 w.	63
second »	36	24	22	29	11	34	33	22	20	—	11	11	6 »	23
third-fourth week	30	42	43	24	50	25	42	19	57	60	60	6	8 »	11
later.....	7	15	5	11	37	4	8	26	20	30	10	1	later	3

Table VII.

Percentage of scarlet fever in different months of year.

Year	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
1890	1.4	2.6	1.8	4.0	8.9	10.6	10.5	13.4	13.3	14.2	8.6	10.7
1913	8.4	3.8	6.1	4.4	5.8	6.7	6.2	9.1	13.4	9.8	13.4	12.3
1937	6.2	7.0	7.3	7.0	2.3	4.2	8.1	10.0	17.8	9.6	11.2	9.3
1938	10.1	6.7	15.8	12.9	9.1	12.5	3.3	3.8	6.2	11.0	5.3	3.3
1939	0.2	0.5	0.9	0.3	0.8	3.5	21.6	10.0	7.7	20.2	24.4	9.9
1945	6.0	4.7	4.7	3.0	6.0	7.0	11.3	7.0	12.0	9.5	13.3	15.5
1946	9.9	8.2	4.3	6.2	7.1	11.8	5.6	6.0	8.2	14.6	8.7	9.4
1947	7.9	6.2	4.7	4.5	5.3	3.2	2.8	4.5	9.7	20.9	17.4	12.9

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between 0.5 and 1.5 per cent, and after penicillin treatment in 0.4 per cent of all cases. The changes were in most cases incidentally and noted in only a single Ecg. The most frequent was inversion of T in one or more leads, next S. T below the base line, and finally prolonged P. Q., arythmia, and extrasystoles in only a single case.

Thus it appears statistically that scarlet fever, in spite of the apparently milder course of the primary disease, may still be regarded as severe in view of the high frequency of complications. The frequency of complications does not seem to be proportional to the severity of the primary disease. This is in accord with a publication of Bjørksten (4) in which an epidemic is mentioned which showed a high frequency of complications in periods with relatively slight initial symptoms.

The good effect of penicillin treatment on the frequency of complications has been pointed out in earlier publications from Norway as well (15, 16). The continuous high frequency of complications proves the necessity of this treatment.

That the complications are due not only to cross-infection during hospitalization appears from the high frequency of primary complications.

The fact that in this material some complications occurred in spite of penicillin treatment may be ascribed in part to the circumstances that isolation in »type wards» or »clean wards» was not always possible, that the patients were not isolated from recent cases after the end of the treatment, and perhaps also that some of them were treated 3 to 4 days only.

Summary

The frequency of mortality, relapses and complications from scarlet fever during 3 epidemics in Oslo in the years 1890—1947 has been investigated in all 5 100 cases. The mortality and relapses have decreased at an equal rate, the mortality from 7.8 per cent to 0.0 per cent and the relapses from 5.8 per cent in 1937 to 0.4 per cent in 1947. The frequency of complications has decreased only with regard to the cardiac complications and nephritis. The material indicates that during all these years the

frequency of the other complications has remained high up to the introduction of penicillin in spite of the fact that the primary course has apparently been milder.

Résumé

La fréquence de mortalité, de rechutes et de complications dans la scarlatine, durant 3 épidémies à Oslo, de 1890 à 1947, a été l'objet d'un examen, en tout 5 100 cas. La mortalité et les rechutes sont également regressives, la mortalité de 7.8 % à 0.0 % et les rechutes de 5.8 % en 1937 à 0.4 % en 1947. La fréquence des complications ne diminue que dans les cas de complications cardiaques et de néphrites. La matière d'étude montre que durant toutes ces années jusqu'à l'introduction de la pénicilline, la fréquence d'autres complications est restée constamment élevée bien que le cours primaire de la scarlatine soit devenu visiblement plus bénin.

Zusammenfassung

Mortalität, Recidiv und Komplikationen bei Scharlach während 3 Epidemien in den Jahren 1890—1947 waren Gegenstand einer Untersuchung bei zusammen 5 100 Fällen. Mortalität und Recidive haben gleich viel abgenommen, die Mortalität von 7.8 % zu 0.0 % und die Recidive von 5.8 % 1937 zu 0.4 % 1947. Die Häufigkeit der Komplikationen verminderte sich nur in Bezug auf Herzkomplikationen und Nephritiden. Das Material zeigt, dass die Häufigkeit anderer Komplikationen in allen diesen Jahren bis zur Einführung des Penicillins anhaltend hoch ist trotz der Tatsache, dass der primäre Verlauf des Scharlachs offensichtlich leichter geworden ist.

Resumen

Se ha examinado la frecuencia de mortalidad, relapsos y complicaciones a causa de escarlatina, durante tres epidemias que hubo en Oslo entre 1890 y 1947, en total 5 100 casos. La mortalidad y los relapsos disminuyen (mortalidad de 7.8 % a 0.0 % y relapsos de 5.8 % en 1937 a 0.4 % en 1947). La frecuencia de complicationes disminuye por lo que toca a complicacio-

nes cardíacas y nefritis. El material examinado muestra que la frecuencia de las otras complicaciones ha sido muy alta hasta la introducción de la penicilina, a pesar de que el curso primario de la escarlatina es aparentemente más suave.

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CASE REPORTS

Paroxysmal Ventricular Tachycardia with Subsequent Myocardial Lesion

By

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In recent years paroxysmal tachycardia has figured largely in the literature, a study of which reveals that it is not at all an uncommon disease in children. Paroxysmal (pa.) tachycardia (ta.) is an alarming condition which fortunately, however, seldom leads to death, and when exitus does occur, it is generally due to some underlying heart disease, the tachycardia being but a symptom. To determine the underlying disease or ascertain whether the attack has befallen an otherwise sound heart is of paramount prognostic import. Besides this it is equally momentous to recognize the deviating course this disease pursues in infants. In infants the onset is generally non-characteristic and attended by anorexia and slight general distress, but the disease may lead to rapidly developing circulatory insufficiency. Other factors essential for the establishment of the prognosis are the position of the pacemaker and the duration of the attack. The three types of paroxysmal tachycardia; auricular, nodal, and ventricular have different mechanical effects on the function of the heart. The natural cooperation between the contractions of the auricle and the ventricle is least disassociated in auricular tachycardia, while in nodal tachycardia superimposition, "Vorhofspropfung" (WENCKEBACH), with congestive failure quickly arises. In ventricular tachycardia the contractions of the atrium and the ventricle are often of different rate and varying cooperation. A prolonged attack of tachycardia must surely injure the myocardium and possibly lead to a deleterious dilatation of the heart and to circulatory insufficie cy. As shown by REIN, tachycardia increases the oxygen need of the heart considerably and the shortened diastole during tachycardia exercises a concomitant, unfavourable effect on the filling of the heart, especially on that of the coronary vessels, which might in turn lead to a myocardial lesion of a previously sound heart. A case in which ventricular tachycardia seems to have given rise to myocardial involvement is presented below.

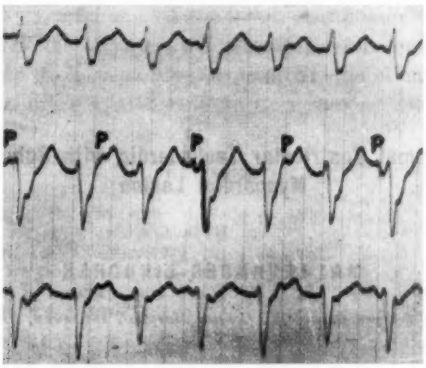

Fig. 1. Ekg. taken by admission. Regular auricular rhythm, rate 130/min. Regular ventricular rhythm, rate 195/min. QRS abnormal, 0.11—0.12 sec. T pos. D.: Ventricular, paroxysmal tachycardia with independent auricular rhythm.

Case history.

Journal No. 387/46. Girl. 8 years old. Visited the outpatient department complaining of pains in the stomach, vomiting and fever. She had hitherto been healthy except for double-otitis two months earlier, which had in the meantime healed completely. Since the disappearance of the otitis she had on various occasions had fever up to 39° C., pains in the umbilical region and vomiting attacks. No soreness of the throat nor pains in the joints. The patient now sought medical advice for similar symptoms with fever varying between 37 and 39 degrees C.

On examination the girl was found to be normally developed for her age and in a very good physical condition. No cyanosis or dyspnoea, no edema. The anamnesis directed attention immediately to the abdomen, which was quite soft, tender nowhere, and apparently void of palpable swellings. The urine was free of albumen and the sediment was normal. Routine heart auscultation divulged tachycardia with a regular rate of 180—190 p/m. Ictus cordi was palpable in I 5 immediately inside the left mid-clavicular line. The tones seemed to be clear. Pulm: 0. Throat: pale with rather small, splitting tonsils. The E. C. G. was taken the same day (Fig. 1), and revealed a regular ventricular rate of 190. The QRS-complexes were widened, 0.11—0.12″, and were very similar to those peculiar to an unusual bundle-branch block (WILSON). T-waves pos. P-waves had a regular frequency of 125 p/m., thus two thirds of the ventricular rate. They reappeared in regular timed relationship to the ventricular complex, so that one complex was preceded and the other followed by a P-wave, while the third QRS-complex was void of P-waves.

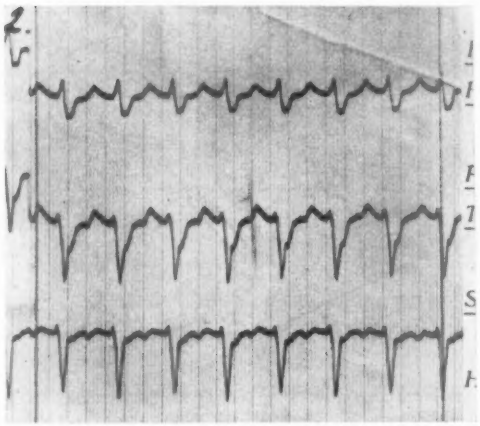

Fig. 2. Ekg. taken at 8 o'clock on the day after admission. Ventricular rate 200/min. Each ventricular complex seems to be followed by a P-wave. Probably "Vorhofprofung".

The amplitude of the ventricular complexes varied also conspicuously in these three different constellations, although they were similar in configuration.

As the patient was now free of symptoms, nothing was done until the following day, when a roentgenogram of the heart could be taken. The first day she had had fever, 38—39 degrees. The next day a new E. C. G. was taken (Fig. 2) which divulged a somewhat accelerated ventricular rate, but the ventricular complex was unchanged. It was now more difficult to distinguish the P-waves, but in LEAD III they seemed to follow immediately after every QRS-complex. During the X-ray examination the patient suddenly felt faint and became cyanotic, for which reason a doctor present applied carotid pressure. The heart rate fell and the patient soon recovered. The roentgenogram of the heart manifested: »A slight bulge laterally and anteriorly to the pulmonary conus. There was a considerable posterior bulging of left auricle. Heart volume 310 c^3, corresponding to 290 c^3 per square metre of body surface At the time of the examination there existed severe tachycardia of about 220 beats per min. Heavy pulsation of right heart border, normal pulsation of left ventricular border (Sign. ALM).» Some hours later the E. C. G. showed a regular sinus rhythm with a rate of 110 beats per min. (Fig. 3). P-waves pos. P_2 path. high and pointed. P–Q 0.14″. QRS 0.06″, normal configuration. All T-waves inverted and in LEADS II and III extremely deep, S—T_2 distinctly, S—T_3 slightly depressed. The following day the

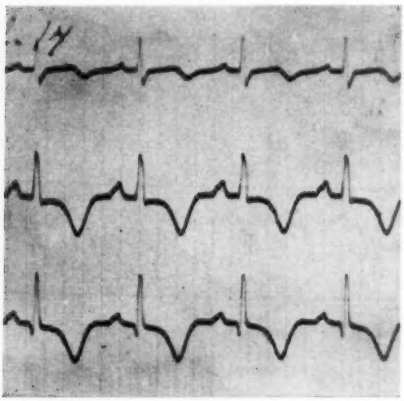

Fig. 3. Ekg. at 14 o'clock on the day after admission. Regular sinusrhythm, 110/min. P pos. P_2 abnormally high. P–Q 0.14 sec. QRS 0.06 sec., normal. T_1 neg., T_2 och T_3 strongly neg. S–T segment depressed in lead II and slightly depressed in lead III.

E. C. G. manifested a rate of 85 beats per min. T_1 was diphasic, depression of the S—T segments was more distinct. The patient was now free of fever and remained so, and she felt so fit that it was only with difficulty that she could be kept in bed. One week after the attack the E. C. G. showed considerable regression. Rate: 65 beats p/m. P-waves normal. T_1 pos. T_2 and T_3 neg. but substantially smaller than before. S—T segments isoelectrical. Q_3 had appeared, was small but distinct. About three weeks after the attack all T-waves were pos. (Fig. 4). Q_3 had increased somewhat more in size. This continued the next few months and Q_3 went up to about one third of the size of the highest R-wave. Otherwise the E. C. G. was unchanged. During about one year's observation the patient has been free of symptoms.

Symptoms.

In this 8-year old child the symptoms were non-characteristic: vomiting, pains in the abdomen, and fever. No subjective heart symptoms unless the abdominal pains were caused by an enlargement of the liver with capsular tension due to congestive failure. Palpation, however, gave no evidence of liver enlargement. Neither could any other signs of insufficiency be discerned except for cyanosis in association with the sudden distress during the X-ray examination, which was probably to be ascribed to the sudden arisal of superimposition. The position of the P-waves in the E. C. G. taken prior to the X-ray examination speak in

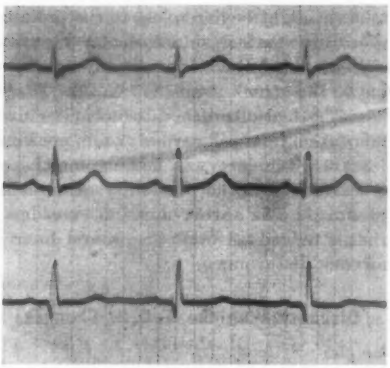

Fig. 4. Ekg. 25 days after admission. S–T segments are now isoel. and P pos. Q_3 marked.

favour of the correctness of this assumption. They follow immediately after every QRS, which heralds a superimposition.

Judging by the anamnesis it would seem as if the patient had had several similar attacks during the previous month. She had recovered quickly and was free of trouble after each attack.

Diagnosis.

The type of tachycardia must be determined by the E. C. G. The nature of the ventricular complex was presumptive of a ventricular pacemaker. According to WARBURG, the ventricular complex may be deformed also in prolonged supraventricular tachycardia on account of fatigue of the conduction tissue. In such cases there ought to be a deformation also after the attack, as there were other signs of myocardial involvement. The independent auricular rhythm also spoke very much in favour of ventricular tachycardia, which seems to be the most uncommon type in children. In 1942 ROSENBAUM et. al. (15) could trace only seven cases under 15 years of age in the literature.

Etiology.

Ventricular tachycardia is more often associated with heart diseases such as, myocarditis and coronary occlusion, than are auricular and nodal tachycardia. In the case under discussion myocarditis might have existed subsequent to otitis, which the patient had had a few months before. It is difficult to draw any conclusions in this respect from an E. C. G. taken after an attack. The myocardial lesion registered by the E. C. G.

is of such nature that it might be due solely to the prolonged tachycardia. Other signs of myocarditis such as sino-auricular disturbances of conduction are lacking. Neither are there any clinical signs of acute infection. Fever may be due to the attack itself (5, 7 & 12). The temperature and the rate of the heart beat also returned to normal simultaneously. The erythrocyte sedimentation rate was normal, 7 mm per hour, and the white blood cell count 3 200. Evidence was lacking for the establishment of the diagnosis 'myocarditis' but the possibility of sequelae after myocarditis cannot be excluded. The author however considers it possible that the tachycardia has attacked an otherwise sound heart the instigating factor being a nervous disturbance.

Discussion on the E. C. G. Changes

The Auricular Complex.

It is theoretically feasible that P-waves with a frequency equal to two thirds of that of the ventricular complex (Fig. 1) might be ascribed to a retrograde conduction from the ventricle in a patient who has had partial heart block such as occurs in Wenckebach's periods and in which the third auricular contraction is dropped. But the relative occurrence of the P-waves was quite regular, which was naturally presumptive of an independent auricular rhythm. This is also the rule with ventricular tachycardia.

After re-assumption of the sinus rhythm there appeared in LEAD II a pathologically high P-wave (Fig. 3) that returned to normal after the elapse of a week. The same transient change occurring after an attack of tachycardia has been described by KOHBRUK (9), who contends that the changes are due to the existence of a high, sympathetic tone also subsequent to the attack. MANNHEIMER (13) reports abnormally large P-waves in a post-attack E. C. G. of an infant, three weeks old. High P_2 and P_3 often constitute the finding in cor pulmonale, while mitral affections are generally reflected in changes of P_1 and P_2. SCHERF and BOYD postulate that it is uncertain whether the changes are to be attributed to hypertrophy alone or to a dilatation of the auricle. In this case in which P is abnormally high in LEAD II, the changes were probably caused by a cooperation of the auricles in accordance with EINTHOVEN's rule. Hypertrophy could hardly have arisen in this short time, and also the quick return of the E. C. G. to normal seems to indicate that the high P-waves might have been due to a dilatation that disappeared after the rhythm had again become normal.

The Ventricular Complexes.

During the tachycardia (Fig. 1) the ventricular complexes are of unchanged configuration but vary regularly in amplitude with three

orders of magnitude which reappear every third beat. Especially in LEAD III, there occur physiological differences in size during the respiration phase, but this cannot be the cause of this series appearing every second, which would postulate a respiration rate of 60 p. m. On the other hand it might be ascribed to the constellation of the P-waves changing concomitantly with the changing amplitude, possibly by the differential diastolic fillings of the ventricles. LEVINE (cit. ROSENBAUM) found variations in the volume and quality of the first heart tone in cases with different auricular and ventricular rhythms. This is probably another manifestation of the same change in the ventricular activity.

The Terminal Complex.

The E. C. G. taken a few hours after the attack (Fig. 3) has inverted T-waves and depressed S—T segments. In view of the fact that not only the T-waves but also the S—T segments had changed considerably, most distinctly in LEAD II, one might assume the existence of cooperating, general changes in both halves of the heart. In children a general lesion is as a rule least apparent in LEAD I, and it was also in this lead that the E. C. G. first returned to normal. Already the following day T_1 became di-phasic and after another six days positive. By this time also the depression of the S—T segments had disappeared, while T_2 and T_3 were still negative. It was not until after the elapse of another two weeks that all the T-waves were positive (Fig. 4) and the terminal complex thus normal.

What then is this lesion to be attributed to? It seems obvious that it cannot be ascribed solely to myocarditis, because clinically myocarditis of such extent can hardly pursue such a symptom-free course with so quick a regression as in this case.

The changes in the terminal deflections are of the very type characteristic of hypoxia of the heart musculature and often termed coronary insufficiency. They are caused locally by coronary stenosis but may also be due to general anemia, e.g., after acute loss of blood (SCHERF et al., cit. SCHERF and BOYD). The serious circulatory disturbance arising during prolonged tachycardia befalls the coronary circulation most of all. The attack in question, which lasted almost a whole week, is therefore per se enough to bring about hypoxia of the heart musculature and thus explain a myocardial lesion of this order.

Also many cases are known to the literature in which transient changes of the S—T interval and T-waves have occurred subsequent to prolonged attacks of tachycardia and which cannot be explained by any affection of the heart. BURAK and SCHERF (2) describe two otherwise healthy individuals whose E. C. G. taken after an approx. 24-hour attack of tachycardia displayed either absent or inverted T-waves, which phenomena they interpreted as a serious myocardial lesion. LÁSZLÓ (10) reports a case of a 33-year old woman with repeated attacks of pa. ta.

with subsequent signs of coronary insufficiency, the duration of which increased with increasing prolongation of the attacks. LÁSZLÓ presumes that the changes were incited by tachycardia that caused coronary insufficiency. Also other cases are recorded, and it would seem that the changes may last a few weeks (1, 4, 9, 20, 21, 22).

Therapy.

Only the effect of the carotid pressure will be discussed here. WARBURG states that such compression is never effective in ventricular tachycardia. In most cases of ventricular tachycardia there exists myocarditis or coronary thrombosis. Such cases with organic changes will surely be more difficult to influence with a neural impulse than is supra-ventricular tachycardia, which is often of neurogenic origin. The latter type of tachycardia is instigated by an ectopic pacemaker responsive to nervous impulses. As a rule it naturally lies supraventricularly, where the stimulating tissue gives a more potent impulse that decreases with increasing distance from the sinus node. In the case in question the pacemaker is intraventricular, but the etiology and thus also the therapy for this ventricular tachycardia of an otherwise sound heart seems to be the same as for the supraventricular tachycardia. This ventricular ta. must thus be influenced by the same changes in vegetative tone as the latter. RUBELL and STRAUSS (16), after a perusal of the literature on ventricular ta., mention three cases in which the attack was arrested by carotid pressure or by a change in the posture of the patient. Owing to the anatomical distribution of the vagus a stimulation of the nerve cannot have any direct effect on the ventricle. An indirect effect of acetylcholine via the blood passages however seems feasible.

Prognosis.

The sudden deterioration in this case confirms the fact that the prognosis of every case of pa. tachycardia, especially when of prolonged duration, must be considered as doubtful. Superimposition can lead to quick congestive failure, and myocardial anoxemia during attacks to myocardial lesions.

Summary

A description of a case of ventricular tachycardia with independent auricular rhythm in an 8-year old girl with an otherwise probably sound heart. After a period with but sparse symptoms, the patient suddenly becomes cyanotic. Carotid pressure is applied and the sinus rhythm occurs. After the attack changes in all leads of the terminal complex of coronary insufficiency type were discernible. The author considers these changes to be presumptive of a myocardial lesion due to hypoxia during

attacks. Changes in the amplitude of QRS, a transient increase in the height of P_2 and the effect of the carotid pressure are also discussed.

I wish to express my sincere thanks to Dr. GÖRAN GEZELIUS, the present chief of the pediatric dept., Central Hospital, Östersund, who followed up the patient and kindly permitted me to inspect the records and E. C. G.

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A Case of Tuberculous Hepatitis and its Biological Reactions

By

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and

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K. D., aged 14 (No. 35087), was admitted to this Clinic on February 24, 1948, transferred from a Clinic in Corinth.

His family history was good and his past history of sickness showed nothing unusual. The current history revealed that the patient had been well until the month of December, 1947, when the first signs of the disease appeared. He felt indisposed and his temperature was low. Towards the end of December he developed a higher temperature and pain in the right hypochondrium not referred elsewhere. His temperature remained high (37.5°—40° C.), obliging him to stay in bed. Besides the aforementioned symptoms, he complained of complete loss of appetite, feeling disgust even at the sight of food. At this stage an examining physician found no symptoms except apparent liver enlargement. 1 000 000 I. U. of penicillin were then administered but without effect. As a liver abscess was suspected, an exploratory puncture of the posterior surface of the organ was made on January 26, 1947. The results were negative. Still with no change in temperature, the patient was admitted to a surgical clinic in Corinth on February 2, 1948. Clinical examination by Dr. Dalacopoulos of Corinth Clinic revealed no respiratory or other systemic disorders but an enlarged liver extending in the anterior axillary line (R) from the fifth rib to one and one half inches over the anterior superior iliac spine and two inches over and to the left of the umbilicus. The whole enlargement was painless except for the part lying in the fifth intercostal space and on the anterior axillary line. An X-ray of the liver showed a normal upper margin and a lower margin reaching one and a half inches below the posterior superior iliac spine. A blood test showed WBC 21 000; polymorphonuclear cells 80 %. The urinalysis was normal but the temperature high, swinging between two degrees Centigrade. No mention was made of jaundice or other symptoms from the liver. Penicillin was again administered (800 000 units), but again without any effect whatsoever on the condition of the patient. However, as the high

temperature was persistent and a second exploratory puncture negative, an exploratory laparotomy was decided upon and performed on February 14, 1947. This revealed a reddish parietal peritoneum, while the visceral peritoneum, gall bladder, transverse colon and omentum were normal. The liver was darker than normal, with a rounded margin and a surface covered with yellowish-white streaks with lentil-shaped nodules the size of a walnut. A piece of the liver tissue was taken for biopsy by Prof. J. Katsaras, Director of the Pathological Laboratory of Athens University; the patient was registered as No. 2221. The *biopsy* proved *tuberculosis. Disseminated caseous tubercles were found; the rest of the parenchyma showed signs of blood stasis and intense fatty infiltration.* Following the operation the general condition of the patient improved and his temperature dropped considerably. Ten days afterwards, however, he was again admitted to this Clinic, still feverish.

Examination revealed an individual of normal physical development, body weight 29 kilograms, height 1.42 meters, but anemic and undernourished. The respiratory system showed dry râles in the bases of both lungs. The circulatory system showed a soft pulse and heart beats were faintly heard. The tongue was coated. The abdomen showed a horizontal scar 10 centimeters long starting from the middle of the epigastrium and leading to the right hypochondrium. The liver was enlarged and smooth in outline, extending three inches below the floating ribs, with a diffuse sensitivity to palpation and percussion. Murphy's sign was negative, and the spleen was not palpable.

Laboratory Findings. Blood: red blood cells 3 600 000; white blood cells 17 800. Type: polymorphonuclear 86 %, lymphocytes 7 %, eosinophiles 5 %, large mononuclear 2 %. *Examination of urine:* normal. *Bile salts and pigments:* negative. *Mantoux reactions* (1 : 10 000 and 1 : 1 000): negative. *X-ray of lungs:* normal. *Erythrocyte sedimentation rate* (Westergren): 1 hr. 140, 2 hrs. 145, 24 hrs. 150. The *glucose tolerance test* (an intravenous injection of 30 cc of glucose) showed a great delay in the ascending line of the curve and prolongation of the descending line. Its peak (184) was reached after 90 minutes. Course of the curve: 0.84; 30 minutes 1.53; 60 minutes 1.68; 90 minutes 1.84; 120 minutes 1.60; 150 minutes 1.01. The *specific gravity test for liver function* (Volhard's) was normal, the *cerebrospinal fluid* was normal, and the *blood culture for Koch's bacillus* was *positive*. The *lipase test* (Comfort-Osterberg) gave a reading of 0.58 cc from a dilution of N 20 NaOH.

Progress of the Disease. From February 24—29, 1948, the patient showed no improvement; he was on a carbohydrate diet with plenty of fruit. On March 5, 1948, streptomycin treatment was instituted, with 0.80 g (4×0.20) of streptomycin daily. After four days' treatment the temperature began to subside and returned to normal, where it has

remained since. Appetite improved considerably and protein was added to the diet, which was gradually made normal. The patient's weight increased gradually. The administration of streptomycin continued for two months (March 1 to May 1, 1948), dose 0.20 g four times a day for twelve days, later 0.10 g six times a day. The total dose given was 45 g. As has already been stated, the result of the drug was a definite improvement in the patient's condition. The enlargement of the liver began to subside and twenty days after the patient's admission, i. e. after two weeks of treatment, it was identified about an inch below the lowest rib in the mammary line, where it remained until the patient's discharge.

Progress of Biological Reactions

1) Tuberculin Reaction[1]:

February	25, 1948	1 : 10 000	negative
March	7	1 : 10 000	»
	23	1 : 1 000	»
	29	1 : 100	»
April	2	1 : 1 000	»
	11	1 : 10 000	? positive
	19	1 : 10 000	definitely positive ++

2) Erythrocyte Sedimentation Rate (Westergren)[1]:

February	26, 1948	1 hr. 140,	2 hr. 145,	24 hr. 150
March	7	120	140	145
	24	125	130	135
April	14	130	140	145

The parents refused to allow more blood to be taken after the child appeared to have recovered. Thus we have no later E. S. R.

The patient was discharged from the Clinic on May 2, 1948, as clinically cured. By that time his body weight was 35 kilograms, i. e. an increase of 6 kilograms, and the tuberculin reaction was positive. The diagnosis was that of primary tuberculosis of the liver clinically diagnosed and effectively treated with streptomycin.

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[1] A control examination performed on July 9, 1948, gave the following results:

E. S. R. (Westergren):	90—115—135
Mantoux (1 : 10 000:	weakly positive.

Comments

This case is being published for the following important reasons:

I. It constitutes a rare form of localization of tuberculous infection in the liver. It is well known that the liver participates in the generalization of the disease, and necrotomy of patients who died of miliary tuberculosis has revealed the liver to be full of tubercles. However, single localization of the disease in this organ as its primary clinical manifestation has been only rarely described. For the writer, who is particularly interested in tuberculosis of children, this is the first case he has met. There may have been others which escaped diagnosis and this case would not have been diagnosed without exploratory laparotomy. As the history of the case shows, the clinical picture of the disease suggested rather an acute hepatic abscess with liver enlargement, high remittent fever, and leucocytosis but no jaundice. What the progress of the disease would have been without the institution of streptomycin treatment is difficult to tell. In studying the available bibliography, we have to differentiate this case from the cases of liver enlargement which we meet very often during the course of the primary syndrome and which are sometimes associated with jaundice. We have already met several such cases. In miliary tuberculosis, when necrotomy shows the liver to be full of tubercles, the principal form taken by localized tuberculosis of the organ is solitary abscesses (Sheldon 1) with the characteristic periodic symptom of jaundice. This form is considered most common in children (Ticcozzi 2). Several other forms of multiple large-node tubercles have been also described and, less often, single tubercles with extensive sclerosis of the organ and with ascites, which are associated with tuberculosis of the mesenteric glands (Keller and Moro 3, p. 763). The case under discussion may be compared with no other known case, at least in the stage in which it was diagnosed; it might have developed into one of the above varieties if it had not been treated with streptomycin. This case rather suggested acute inflammation of the liver.

Etiology. It is most probable that the disease originated in the bowel (Fischer 4) and that the infection spread through the portal vein (Strauss 5).

Morbid Anatomy. According to Orth 6, the miliary forms of tuberculosis of the liver are characterized by very small tubercles of greyish color; tubercles near the bile passages are greenish. Kaufmann writes that the smallest of the tubercles are infiltrated with lymphocytes and the largest contain a preponderance of epithelioid cells. As the disease progresses and the number of tubercles increases, many nodules surrounded with fibrous tissue are formed (Pagel 7). After caseation of the

large nodes, which may reach the size of a filbert, the consistency of the liver tissue resembles dry cheese. Caseation may cause formation of cavities which are often found to contain masses of hard bile substance.

II. *Course of Biological Reactions.* The progress of these reactions is remarkable. On the patient's admission the tuberculin test (1 : 10 000) was negative. A more potent dose (1 : 100) of tuberculin also gave a negative reaction. It was only after approximately 45 days of streptomycin treatment and considerable improvement on the part of the patient that the reaction became positive. The absence of reaction in this case is interesting for the following two reasons: a) from the point of view of diagnosis. A negative reaction, even in a patient 14 years old, would necessarily remove suspicion of specific disease, especially since the respiratory system gave no significant symptoms. The literature supplies no information. Fissinger (8) states only that the tuberculin reaction becomes negative in epidemic catarrhal jaundice but later changes to positive. It is certain that the tuberculin reaction is intensely positive in liver enlargement in the primary syndrome, as in miliary tuberculosis. In this case, however, its absence made diagnosis problematic. It was only after improvement of the patient with streptomycin that the tuberculin reaction became positive, as is always the case with negative reactions[1], and this after a very long time, the longest we have ever seen. In the advances stages of miliary tuberculosis, the tuberculin reaction usually becomes positive again less than a month after the beginning of treatment.

b) In this case the tuberculin reaction, besides being of diagnostic value, is interesting from the point of view of general biology. There is no literature available to help us see whether this is a single observation or connected with every form of tuberculosis of the liver. However, the absence of the tuberculin reaction in a severe form of tuberculosis of the liver is of value in studying the problem of allergy and the part which this organ plays in it. In other words, it concerns the problem of the relation between the function of liver, and especially of the reticulo-endothelial system, and the function of allergy. Herxheimer states that an increased phagocytosis of Kuppfer cells occurs in tuberculosis of the liver. In the above case the severe disease of the organ caused the fall of its position in the defensive system of the body probably by blocking the functional ability of the reticulo-endothelial system. This has been observed in measles, where the elective action of the causative agent in invading the mesenchyma explains the disappearance of allergy which is determined during the period of rash. We feel that this phenomenon is

[1] The Effect of Streptomycin on Tuberculin Reaction, Streptomycin in the Treatment of TBC of Children, 1948.

of special theoretical value to the problem of allergy in tuberculosis. The absence of the tuberculin reaction in this case is associated with the equally noteworthy fact of increased erythrocyte sedimentation rate. This is the highest count we have obtained in the follow-up of this phenomenon in our tuberculous patients. The persistent increased sedimentation rate in spite of the improvement of the patient is also worth noticing. Our comparative studies of the relation between tuberculin reaction and sedimentation rate have proved that, in most instances, the weaker the former, the higher the latter. It is probable that the change in the liver cells may also play a very important part here, since it is known that the erythrocyte sedimentation rate increases in acute liver disease.

III. *Diagnosis and Treatment.* The above description makes evident the difficulty of diagnosis. The patient gave no other symptom than liver enlargement and remittent fever. Laboratory findings showed leucocytosis, but this did not suggest the symptomatology of a tuberculous infection of the liver. What remained was a blood culture for Koch's bacillus. This was positive. Is this, however, always so? Is the excessively high erythrocyte sedimentation rate of specific importance in this case? We cannot give an answer because we have not made other observations. Consequently, the diagnosis of tuberculosis of the liver would have been impossible in this case but for the exploratory laparotomy. The streptomycin took effect with astonishing rapidity. After four days of treatment, the patient's temperature returned to normal and remained there. What would have become of the patient but for the institution of streptomycin treatment is difficult to say. We are following the patient up. Nevertheless, we feel that for the reasons given above this case is interesting, and we have therefore decided to publish it.

Summary

A 14-year old boy the symptoms of whose disease suggested an acute liver abscess. Laparotomy was therefore performed. Macroscopic examination as well as biopsy proved disseminated tuberculosis of the liver. The following are some interesting points from the examination of this case:

1. A positive blood culture for Koch's bacillus.
2. Negative tuberculin reaction even in a potency of 1 : 100. It was only after streptomycin treatment that a positive reaction was obtained, but still it was not a strong positive reaction (+ +).
3. The high sedimentation rate of erythrocytes.

Certain points of view are given about the importance of the progress of these biological findings.

This case was treated with streptomycin. The total dosage administered was 45 grams. As a result the patient's temperature dropped and his liver symptoms were relieved.

The patient's condition has since been normal to the present time.

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FROM THE CHILDREN'S CLINIC, HELSINGFORS UNIVERSITY
CHIEF: PROFESSOR A. YLPPÖ, M.D.

The Effect of Methylscopolamine-nitrate (Scopyle) on the Stomach in Hypertrophic Stenosis of the Pylorus

(A roentgenological study)

by

PER-ERIK HEIKEL

Ever since in 1942 E. Nyman gave an account, later supplemented (1943, 1944, 1945), of the main effects in principle of methylscopolamine-nitrate (scopyle), this medium has been used quite extensively in pediatrics — mainly in Sweden — in the treatment of hypertrophic stenosis of the pylorus in infants. According to Nyman's investigations, scopyle has an effect which is twice or thrice that of the methyl atropine (Eumedrine) formerly used as a spasmolyticum in these cases. The results which have been published (Elgenmark 1944, Lindberg 1946) seem to show that scopyle has brought about a notable improvement in the internal therapy in this disease.

On the initiative of Docent Räihä, trials have been made since the middle of 1946 in the Children's Department of the Public Hospital in Helsingfors with a drug acting on quite different principles, viz. pilocarpine hydrochloride. Roentgenological observations concerning the effect of pilocarpine of the stomach in hypertrophic stenosis of the pylorus were published by the author in 1947. In order to obtain an interesting comparison between these two mediums, the author has continued these investigations making use of scopyle but in all other respects using the same technique as before.

Technique

Runström's methodics have been those most closely followed in all important points. The patient is fasted for at least 5 hours before the

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examination takes place. The stomach is not rinsed out or emptied before the examination. As a contrast a suspension of Astrabaryte of about 50 % strength has been used. About 50 grammes of this contrast are fed to the patient with a teaspoon. The patient is thereupon placed in a recumbent position on the right side, with a slight turn towards a stomach position, in order to obtain a free projection of the canalis egestorius and pylorus. As in the manifest stage of the disease, it is important that the patients be protected against chills and therefore they have not been undressed but have been examined in their ordinary clothing. They have been kept in the above position during the period of the examination. By this means it has been made as little tiring as possible at the same time that conditions have been established which closely resemble the ordinary physiological ones for the evacuation of the stomach. If examination is made during the manifest stage of the disease the emptying of the stomach is as a rule delayed. At a first exposure a general idea is obtained of the size, form, and peristalsis of the stomach. Should the contrast material have failed to fill the canalis egestorius and the duodenum immediately, exposure has been interrupted and a new control has taken place after a lapse of five minutes. By this means a protracted exposure is avoided. In order to retain the resemblance to normal physiological conditions as far as possible neither compression nor palpation of the stomach have been resorted to. Roentgenograms have been taken when the canalis egestorius and the duodenum have filled for the first time, generally 1 or 2 series of 4 pictures each. The time which has elapsed from the first opening of the pylorus and its width, length, and peristalsis, if any, have been observed and noted. Thereafter the patient has been kept in the same position until $1^1/_2$ hours has elapsed since the contrast meal, whereupon a new examination is made and the quantity of contrast in the intestine compared with the quantity in the stomach. By this means the examiner obtains an idea of the evacuation which experience has shown to be fairly good, although somewhat subjective. An examination of the evacuation after 3—4 hours, when according to the literature (Meuwissen & Sloof, among others) it is complete, has intentionally been omitted, partly in order not to overstrain the patients during the most serious stage of their illness, and partly because experience has shown that after only $1^1/_2$ hours a good idea of the evacuation of the stomach may be obtained. This opinion is also held by Runström. A proof of the comparative mildness of the examination is that none of the patients has vomited in the course of it, a fact which has facilitated determination of the stomach evacuation in a high degree.

Some days after the first examination, a renewed examination has been made after administration of scopyle. The scopyle has been administered sublingually in the form of drops in a dosage of 0.25 mgr. 30 minutes before the contrast meal. This mode of administration cor-

responds closely to the method most suitable for clinical use, although the dosage has been made about double the clinical dose in order to give a clearer picture of the effect of the medium.

The material comprises 17 cases of hypertrophic stenosis of the pylorus which have been cared for during 1947—48 at the Clinic for Children in Helsingfors. The cases consist of an arbitrarily chosen part of all cases admitted during the time in question. All cases have been in a clinically active stage, with violent, cascade-like vomitings, and in 13 of the cases there has also been clearly noticeable ventricular peristalsis in the epigastrium. The first symptoms of the disease have in all instances shown themselves at the age of 0—4 weeks. All cases, with the exception of one, have been treated internally after the examination. In one case an operation was performed a week after the examination. 2 of the cases receiving internal treatment died in consequence of complicating infections. All the remainder, including the operated case, have been discharged as convalescent.

All details of the results are best shown in Table 1. Summing up, it may be said that in 13 cases the strong peristalsis was plainly weakened but in 4 cases not noticeably affected by the use of scopyle. The beginning of the evacuation was improved in 5 instances, remained unchanged in 6, and became worse in 6. The width of the stenosis was increased in 5 instances, remained unchanged in 7, and became worse (probably because of the weak peristalsis) in 5. Evacuation of the stomach over a $1^1/_2$ hour period improved in 4 cases, remained unchanged in 2 and was obviously reduced in 11.

A comparison with the results of pilocarpine medication published by the author in 1947 may be of interest (Table 2).

From this table it appears that pilocarpine increases in a very striking manner the peristalsis of the ventricle, whereas scopyle reduces it; this result was to be expected from a theoretical point of view. The commencement of evacuation and the width of the stenosis were not affected to any extent worth mentioning by scopyle, whereas pilocarpine shows a tendency towards an improving effect in this respect. Most important from the clinical point of view is the fact that the evacuation of the stomach over

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Fig. 1. Case 10 at Control Examination. Strong Peristalsis, Evident Stenosis.

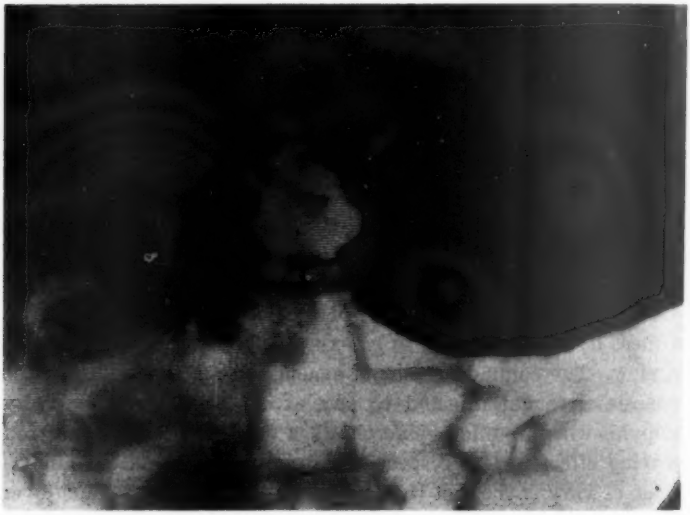

Fig. 2. Same Case After Scopyle Medication. Peristalsis Somewhat Calmer, Stenosis Unchanged.

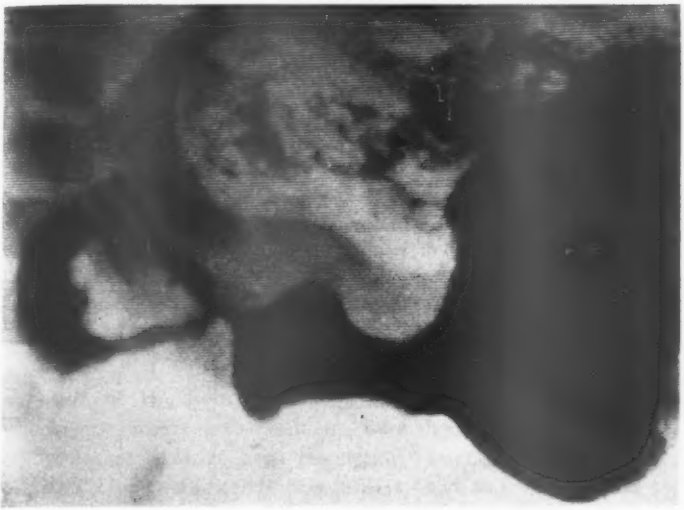

Fig. 3. Case 13 at Control Examination. Strong Peristalsis, Evident Stenosis.

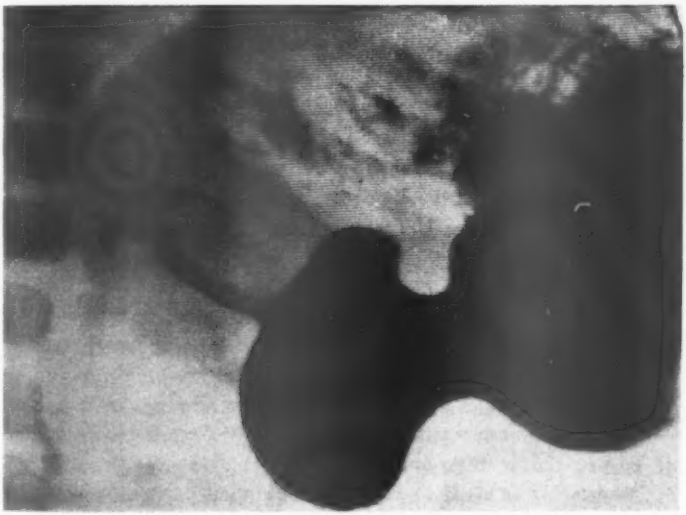

Fig. 4. Same Case After Scopyle Medication. Peristalsis Somewhat Weaker, Stenosis Unchanged.

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Table 1.

Case	Age at Examination	Peristalsis	Opening Time of the Stenosis in Minutes	Width of Stenosis in mm's	Amount Evacuated Within 1½ Hours in %
1. Girl 437/46	2 m.	violent	15	1	50
Scopyle	2 m. 5 d.	weak	5	2—3	50
2. Boy 314/47	2 m.	violent	40	2	10
Scopyle	2 m. 15 d.	weak	5	2	20
3. Boy 315/47	2 m.	violent	5	1	65
Scopyle	2 m. 4 d.	violent	15	1—2	35
4. Boy 316/47	2 m.	violent	5	1	35
Scopyle	2 m. 3 d.	violent	5	1	65
5. Boy 1855/47	1 m. 20 d.	violent	5	1	90
Scopyle	1 m. 25 d.	weak	—	—	0
6. Boy 2983/47	1 m. 15 d.	strong	5	5	65
Scopyle	1 m. 20 d.	weak	5	1—2	20
7. Girl 3075/47	3 m. 7 d.	violent	20	1	20
Scopyle	3 m. 12 d.	weak	5	2—3	90
8. Girl 3500/47	2 m.	violent	5	4	75
Scopyle	2 m. 4 d.	violent	5	5	35
9. Boy 3592/47	1 m. 14 d.	strong	5	2—3	35
Scopyle	1 m. 18 d.	weak	5	3	20
10. Boy 3604/47	2 m.	strong	5	5	65
Scopyle	2 m. 4 d.	weak	5	5	50
11. Boy 4013/47	2 m.	strong	20	3—4	35
Scopyle	2 m. 3 d.	strong	5	4—5	50
12. Boy 368/48	1 m. 24 d.	violent	5	2—3	65
Scopyle	1 m. 27 d.	weak	15	2	50
13. Girl 1409/48	1 m. 15 d.	violent	10	2—3	100
Scopyle	1 m. 19 d.	strong	8	2—3	100
14. Girl	2 m. 4 d.	violent	20	2—3	35
Scopyle	2 m. 7 d.	weak	—	—	0
15. Boy	1 m. 3 d.	violent	5	2	65
Scopyle	1 m. 6 d.	weak	5	2	35
16. Girl	28 d.	violent	10	1	20
Scopyle	1 m.	weak	20	1	10
17. Boy	21 d.	strong	10	1	50
Scopyle	25 d.	weak	20	2	10

Table 2.

Medium	Peristalsis			Beginning of Evacuation			Width of Stenosis			Evacuation During 1 ½ Hours		
	Incr.	Unch.	Weaker	Earlier	Unch.	Later	Wider	Unch.	Narrower	Incr.	Unch.	Reduced
Scopyle	—	4	13	5	6	6	5	7	5	4	2	11
Pilocarpine (Heikel 1947)	17	—	1	6	12	—	12	5	—	14	2	2

a period of $1^1/_2$ hours was strikingly improved by the use of pilocarpine, whereas the influence of scopyle in this respect also seems rather to have been restrictive. In any case, pilocarpine appears to be the better in this respect. The figures given are too small to be statistically binding, but they nevertheless give a clear indication of the possibilities of obtaining an improved internal therapy by the use of pilocarpine or similar preparations in cases of hypertrophic stenosis of the pylorus. The good results obtained hitherto by the use of scopyle may perhaps be explained by the more protracted effect of the latter preparation, so that a longer observation time of say 3—4 hours after the contrast meal might perhaps give a better result as regards the total quantity of contrast passing the stenosis. Docent Räihä will give an account of clinical experiences with pilocarpine medication later.

Summary

A short account of the roentgenologically noticeable effect of methylscopolamine-nitrate (scopyle) on the stomach in 17 cases of hypertrophic stenosis of the pylorus in infancy. The peristalsis of the stomach was weakened in 13 cases, no effect being noticeable with regards to the opening time of the stenosis or its width. In 11 of the cases the quantity of contrast which passed the stenosis over a $1^1/_2$ hour period was less than at the control ex-

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amination. Comparison with an investigation of the use of pilocarpine hydrochloride seems to show that pilocarpine brings about a more evident improvement of the evacuation of the stomach during the same length of time.

Résumé

Un court compte rendu de la radiologie d'un effet notable de la méthylscopolamine-nitrate (scopyle) sur l'estomac, dans 17 cas de sténose hypertrophique du pylore des nourrissons. Les mouvements péristaltiques de l'estomac étaient affaiblis dans 13 cas mais on ne pouvait constater aucun effet au sujet du moment ni de l'ampleur de l'ouverture de la sténose. Dans 11 cas la quantité de contraste qui passe par la sténose en 1 h 1/2 de temps était moindre que lors de l'examen de contrôle. Un examen comparatif dans lequel on s'est servi de pilocarpine hydrochloride semble montrer que la pilocarpine facilite plus manifestement l'évacuation de l'estomac dans le même espace de temps.

Zusammenfassung

Ein kurzer Bericht über den merkbaren Effekt von Methylscopolamin-nitrat (Scopyl) auf den Magen in 17 Fällen von hypertrophischer Pylorusstenose bei Kindern. Die Peristaltik des Magens wurde herabgesetzt in 13 Fällen, in Bezug auf die Öffnungszeit der Stenose und deren Weite konnte kein Effekt beobachtet werden. In 11 Fällen war die Kontrastmenge, welche die Stenose im Laufe von $1^1/_2$ Stunden passierte, geringer als bei der Kontrolluntersuchung. Eine Vergleichsuntersuchung mit Anwendung von Pilocarpin-hydrochlorid scheint zu zeigen, dass Pilocarpin eine deutlichere Verbesserung der Entleerung des Magens während der gleichen Zeit bewirkt.

Resumen

Un breve informe sobre el notable efecto roentgenológico del nitrato metilescopolamina (escopilo) sobre el estómago en 17 casos de estenosis hipertrófica del píloro durante la infancia. La peristalsis del estómago se debilitó en 13 casos; no se notó ningún efecto en cuanto al tiempo de abertura de la estenosis o de su

anchura. En once de los casos la cantidad de contraste que pasó por la estenosis durante un período de 1.1/2 horas fué menor que durante el examen de control. Una comparación con un estudio del uso de pilocarpina clorhidrato parece demostrar que la pilocarpina ocasiona, en el mismo espacio de tiempo, un mejoramiento más evidente de la evacuación del estómago.

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FROM STOCKHOLMS EPIDEMISJUKHUS. (HEAD: J. STRÖM, M. D.)

Penicillin Treatment of Carriers of Diphtheria Bacilli

by

GÖSTA ÖBERG

The term "carriers of bacilli" is applied to persons who, although infected with pathogenous bacteria, show no symptoms of illness resulting therefrom. In principle they may be divided into 3 groups, viz: convalescents recovering from an illness who still have the bacteria present in the organism; healthy, socalled "contact" carriers; and infected persons whose illness is still in the incubation stage. As far as diphtheria is concerned, this latter group may be neglected entirely. To distinguish convalescent carriers with any degree of certainty is difficult. The diphtheria symptoms may have been very slight or non-characteristic and the diphtheria bacilli may have been discovered later during an examination of environment, although the person in question has been free from clinical symptoms.

Fortunately the number of bacilli carriers in Sweden is not great. The intensive measures used to track them down and the regulations with regard to their isolation mean, however, that a very large percentage of carriers are treated in hospitals for infectious diseases. Isolation carried out in this manner is an essential step in the prophylaxis of the rest of the community. It means however a serious incursion in the freedom of the individual concerned and for the community at large a valuable hospital bed is being taken up. Accordingly, the problem is how to cut this period of isolation to a minimum while at the same time ensuring that the sources of infection will be dealt with effectively.

The number of different methods of treatment that have been used in dealing with these carriers of bacilli is indeed impressive. All forms of local treatment with antiseptics have been

found to be ineffective. It has been observed that an intercurrent illness such as angina may cause a carrier's diphtheria bacilli to disappear. This has resulted in attempts at fever therapy treatment and these have apparently been successful to a certain degree (SARELMA 1946). Attempts have also been made to transfer staphylococcus culture to the tonsils of the carrier, in the hope that this would retard the growth of the diphtheria bacilli (LESBRE & MERLE 1947). Further local treatment with thyrothricin has been reported to give good effect (TURPIN *et al.* 1947). The author has tried this treatment in only 3 cases, all without success.

In many papers tonsillectomy has been shown to be a relatively effective method of treatment. From Stockholms Epidemisjukhus successful results are reported by BERGMAN and FRISELL (1945). An operation of this kind cannot, however, be regarded as a normal method of treatment. Moreover, except as a last resort, the removal of otherwise healthy tonsils cannot be considered justifiable.

FLEMMING (1929), CHAIN *et al.* (1940) and ABRAHAM *et al.* (1941) have shown that penicillin retards the growth of diphtheria bacilli. Many cases have been reported in which penicillin treatment has been used for acute diphtheria. TURNER (1941), MCSWEENY (1945), HERREL (1945), WEINSTEIN (1947), HAADEM (1948) and others have found that the diphtheria membranes and the diphtheria bacilli disappear more rapidly than when there is no such treatment. No other effect on the clinical course has been noticed. In other words, the toxic complications are the same. In a survey from Danzig (WSZELAKI & HANDZEL 1948) the mortality figures appear to have decreased with penicillin treatment. However, the explanation may be that the penicillin prevented streptococcus complications, which are by no means unusual. That these complications often lead to fatal results seems quite probable. LASSEN *et al.* (1948) have shown that streptococci occur in the organs of persons who have died of diphtheria.

Several accounts of the effect of penicillin on carriers of diphtheria bacilli have been published. MELIN (1945, 1946) obtained encouraging results using combined local and intramuscular

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treatment. It seemed as though the local treatment by itself would not give a satisfactory result. Many reports indicate that intramuscular treatment has no or only a temporary effect (SKINNER 1945, THRIFT 1945, PETERSON, NORTHROP and HERREL 1945, KOCHER and SIEMSEN 1946 and LEVY 1948). On the other hand, Weinstein, for example, reports that a chronic carrier of bacilli may be freed of his bacilli if given an adequate dose of penicillin (240 000 units per day for a period of 12 days). Summing up, one may say that opinions regarding the effect of penicillin treatment on carriers of diphtheria bacilli vary. With a few exceptions, the material published covers relatively few cases, the doses given — considering the relative resistance of the diphtheria bacilli — have often been small, the time of treatment has sometimes been short, and check-up following treatment has not always been consistently carried out. The material has not been divided on the basis of whether the bacilli were found in the pharynx or the nasal passages. To some extent this may possibly account for the divergent results. Accordingly to try and find a suitable method of treatment the carriers of diphtheria bacilli sent to Stockholms Epidemisjukhus (Stockholm Public Hospital for Infectious Diseases) since 1946 have been treated in accordance with definite principles. The results obtained so far are described below.

The material covers 98 bacilli carriers who, as far as is known, never had clinical diphtheria, or who had the acute illness at least 6 weeks previously and in most cases earlier still. 87 had the type known as mitis, 1 had intermedius and 10 had gravis. At the commencement of treatment, 51 were found to have virulent bacilli and 47 non-virulent bacilli. In a couple of cases there was a change in the types. A change from virulent to non-virulent and vice versa was not uncommon. This problem will be dealt with more fully further on.

The treatment consisted of intramuscular injections, the duration and the size of the doses being varied. This is shown more fully in the tables. In a few cases described separately aerosol treatment was used. *Nasal and pharynx samples* for cultures according to the methods of Löffler and Clauberg were taken

every third day. *Determination of the type and virulence* was generally carried out every second or third week or when positive cultures appeared after a succession of negative cultures. *The resistance of the bacteria* to penicillin was determined by the cup method (*Heatly* 1944) for all patients and repeated every third week. In a few cases the penicillin concentration in the blood was also determined. The blood samples were taken by an experienced nurse. Microscopic examinations of cultures obtained by Löffler's method were made by the doctors attached to that particular section of the hospital. The other bacteriological examinations were made by Sjukhusdirektionens Bacteriological Laboratory in Stockholm.

The treatment was regarded as successful and the patient discharged if 4 consecutive Löffler and Clauberg cultures taken every third day after the termination of the treatment proved to be negative providing also the patient had a negative Löffler culture on the day of discharge. As will be shown later, this does not invariably mean the same thing as absolute freedom from bacilli, and for that reason it was stipulated in some cases that there should be 5 consecutive negative cultures after termination of treatment. Except when complicated illnesses made it necessary, the patients were not isolated from one another either during or after the termination of treatment.

To illustrate the effect of the treatment the results have been coordinated in tables and diagrams.

Diagram 1 shows all 117 treatments given the 95 patients who received intramuscular treatment (2—8 doses per 24-hour period). In all cases the cultures were positive when treatment was begun. Negative cultures began to appear during treatment. A large percentage of the patients were freed of bacilli during the course of treatment. Quite naturally, more negative tests were obtained with the second than with the first culture after the commencement of treatment. The third culture was not obtained in every case, as some patients received only 6 days' treatment. This explains why this particular column in diagrams 1 and 2 represents only 83 cultures. When treatment was discontinued the number of positive cultures began to increase. In other words, from some

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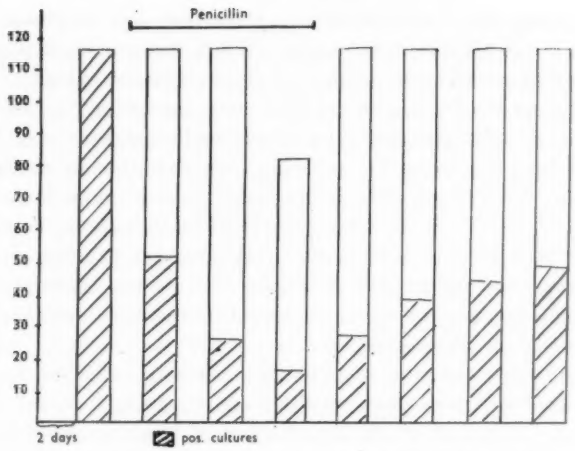

Diagram 1 shows the distribution of positive and negative Clauberg cultures before, during and after treatment.

patients who had given negative tests during treatment it was again possible to cultivate diphtheria bacilli. The increase in the number of positive tests from the first to the second cultivation was 10, from the second to the third 5, and from the third to the fourth 4. Thus it would seem that there is little risk of positive cultures appearing after 4 nasal and pharynx tests taken every third day have proved negative. In 18 cases where patients had negative tests for 4 consecutive cultures after termination of treatment, a fifth culture was made after a further 3 days. This culture was positive in 4 cases in all of which the patients had previously been found to have both nasal and pharynx bacilli. The effect of treatment on these carriers of nasal bacilli was obviously less successful, and in Diagram 2 the material has been split up on this basis.

Diagram 2 shows that the results of the treatment were considerably better in the cases where bacilli were found to be present only in the pharynx test. The less favourable prospects of obtaining freedom from bacilli in the case of the nasal carriers resemble conditions in persons who have not been treated.

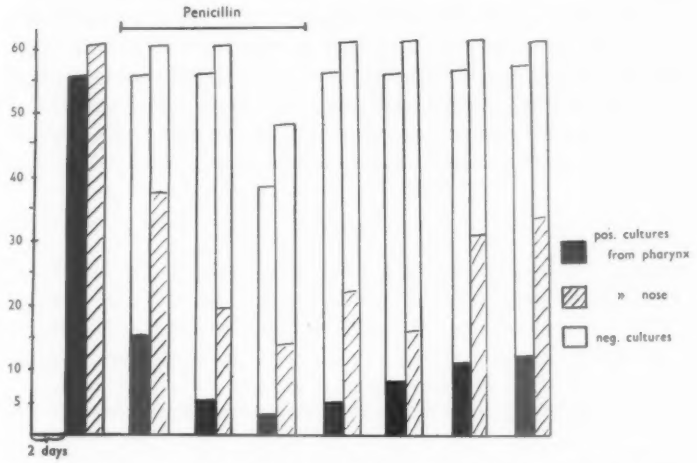

Diagram 2 shows the distribution of positive and negative Clauberg cultures before, during and after treatment and the different results obtained with positive cultures from the pharynx only or from both the pharynx and the nose.

The size of the dose of penicillin has varied. At the beginning 6—8 doses per 24-hour period were given over a period of 6—10 days. The size of each individual dose varied from 2 500 to 60 000 units, according to the age of the patient and the relative resistance shown by the bacteria. The material gives no indication of any difference in the percentage of negative cultures during and after treatment when the period of treatment was from 6 to 10 days. This may be seen from Table 1.

Table 1.

Using the same dose there is no significant difference in the results of treatment over 6 or 10 days.

Number of Doses	Treatment	Cultures During Treatment		Cultures After Treatment	
		Number	% Neg.	Number	% Neg.
6—8	6 days	53	86	104	74
6—8	10 days	139	86	188	79

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On account of the encouraging results obtained with only 2—3 injections per 24-hour period in cases of scarlatina and other haemolytic streptococcus infections (STRÖM 1948), an experiment was made using 30 000—180 000 units 2—3 times per 24-hour period. As may be seen from Tables 2 and 3, the results were clearly worse than when 6—8 doses were used.

Table 2.

Negative cultures during and after treatment with different number of doses daily. The table shows the different results of treatment for persons with pos. throat cultures only at the beginning of treatment and those with pos. cultures from both the throat and the nose.

Number of Doses	Positive Cultures	Cultures During Treatment		Cultures After Treatment	
		Number	% Neg.	Number	% Neg.
6—8	Throat	97	96	148	92
6—8	Nose	95	82	144	60
4	Throat	20	90	20	100
4	Nose	24	25	24	50
2—3	Throat	42	61	52	65
2—3	Nose	54	46	70	50

We next tried 4 doses per 24-hour period, with 80 000—200 000 units per dose. At the same time it was agreed upon that at least 3 negative cultures should be obtained in the course of treatment before it was interrupted. As a result, the time of treatment was generally longer than had previously been the case. The results are shown in Tables 2 and 3, from which it will be seen that the effect of the treatment appears to be the same as when a larger number of doses were employed. However, the material in this group is so small that one naturally cannot draw any definite conclusions following comparison between this and the other tables showing dosing. In cases where the first treatment had no effect, the dose was generally increased and a new treatment used. As Table 3 shows, in some cases it was possible to obtain freedom

from bacilli after the third treatment even when earlier treatments failed. No more than 3 treatments were included in the material. Of course, one must take into account the fact that some of the patients who were treated several times might have become free of bacilli during the same space of time even if they had not received treatment.

Table 3

shows that treatment with 4—8 doses daily is more successful than with 2—3 doses only. It is also apparent that most of the successful cases are free from bacilli after the first treatment. The results of the treatment of carriers with positive cultures from the throat only are better than those obtained for carriers with positive cultures from both throat and nose.

Number of Doses	Pos. Cultures		Number of Cases	Number of Cases Free from Bacilli After			Successful Treatment %
	Throat	Nose		1st Treatment	2nd Treatment	3rd Treatment	
4—8	+	—	31	25	3	1	93
4—8	+	+	32	11	4	2	53
2—3	+	—	9	4	2	1	78
2—3	+	+	13	1	1		15

In Table 3 the patients have also been classified according to dosing and the occurrence of bacilli. It will be seen that with 6—8 and 4 doses it was possible to obtain freedom from bacilli in 93 % of the pharynx carriers. In the cases where bacilli were found in nasal tests as well, the treatment was effective in only 53 % of the cases.

A number of earlier reports stress the importance of distinguishing between virulent and non-virulent bacilli when judging the effect of treatment. A large number of the persons included in the material presented here had non-virulent bacilli at the commencement of treatment. As Table 4 shows, there appears to be no difference in the effect of the treatment on carriers of

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Table 4.

Of the whole material, composing 95 carriers, there seems to be no difference in the treatment of the carriers with virulent or non-virulent bacilli.

Virulence	Positive Cultures from Throat		Positive Cultures from Nose	
	Number of Cases	Successful Treatment %	Number of Cases	Successful Treatment %
Virulent	33	90	18	35
Non Virulent	15	80	32	40

virulent or non-virulent bacilli. I shall return to this question in the discussion later on.

The resistance of the diphtheria bacilli to penicillin was determined at least once in all patients, and in some cases several times. In all tests it was found that complete retardation did not occur until 0.5—2 O.u./c.c. In view of the procedure used these values must be regarded as relative. The solution of penicillin infuses into the culture medium and the concentration of penicillin consequently must be lower in the limit of retardation of the bacterial growth. Compared with other bacteria sensitive to penicillin, however, the types examined here have shown themselves to have a fairly high resistance, or at least to be less sensitive. No definite increase in resistance during the course of treatment could be observed.

Of the 19 patients who had at least 3 consecutive negative cultures during the course of treatment, 15 became definitely free of bacilli in conjunction with treatment. The 4 unsuccessful cases were all nasal carriers, 3 of whom had local complications. (Chronic reropharyngitis, palatoschisis, oesophageal stenosis with nasal tube.)

Apart from what is accounted for in the tables, 6 cases were treated with waxpenicillin. 5 of these were freed from bacilli in conjunction with the treatment. In none had bacilli been found in tests taken from nasal passages. 4 cases previously treated

with penicillin without effect were also given a procain penicillin with a retarded effect made by Kärnbolaget in Stockholm. Only one of the patients became free of bacilli in conjunction with this treatment.

Penicillin-aerosol (inhalation of 10 000 units during a 10 min. period 3 times daily) was also tried in 4 cases. Administered in this way the penicillin is resorbed extremely well and in addition a local treatment of the mucus membranes is achieved. 2 of the cases were freed of bacilli. The result is particularly encouraging in that the patients had showed a resistance to treatment, a resistance in all likelihood connected with chronic, atrophic rhinopharyngitis.

Comments

The investigation confirms previous experiences of the effectivity of penicillin against diphtheria bacilli, even in vivo. The treatment may be successful even with intramuscular injections alone. The great excess in the number of negative cultures that appear in the course of the treatment can hardly be explained in any other way. It is theoretically possible that these negative cultures are due to the fact that the penicillin concentration in the secretion from the mucus membranes of the pharynx and nasal passages is so great at the time of the test that it retards the growth on the bacteriological medium. However, as the negative cultures in a large percentage of cases continued even after termination of treatment, this must mean that the life force of the bacteria has been retarded. In the successful cases, therefore, this retardation must have resulted in freedom from bacilli.

As the diphtheria bacillus shows relatively marked resistance to penicillin compared with the haemolytic streptococcus, for instance, a fairly high blood concentration must be obtained before the parenteral treatment can be expected to show any results. Naturally, therefore, the individual dose of penicillin must be relatively great. Clinical experience shows, however, that it is quite possible to obtain freedom from bacilli even when the dose of penicillin produces a blood concentration that, judged

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by resistance determinations, could not be expected to have any effect. This may be explained at least in part by the fact that the method used for determining the resistance gives only the relative value of the penicillin strength necessary for complete retardation of growth. In all probability, treatment should be extended over a sufficiently long period so that it is possible to obtain nothing but negative cultures during 10—14 days before finally being broken off. The use of depot penicillin would seem to be a suitable means of obtaining an even blood concentration. However, in doing this it is difficult always to obtain a high blood concentration.

As the patients were not usually isolated from one another while at the hospital, one cannot, of course, exclude the possibility that those who were free of bacilli at the end of the treatment became re-infected while awaiting discharge. There may be some indication of this in the fact that not infrequently a change from non-virulent to virulent bacilli was observed. However, in all cases except one these changes were not followed by clinical symptoms. The exception was a 5 year old girl who had non-virulent bacilli at the beginning; later on virulent bacilli and clinical diphtheria appeared. A large number of the carriers of non-virulent bacilli included in this material were discovered through an examination of environment in connection with cases of clinical diphtheria. It is quite possible, therefore, that a number of the cases included were infected with types of diphtheria bacilli that were quite harmless even for their surroundings. On the other hand, it is true that not infrequently changes from non-virulent to virulent bacilli have been observed with patients who have been completely isolated from one another. In the case of one patient with leprosy who was also a carrier of diphtheria bacilli, no fewer than 8 changes from non-virulent to virulent bacilli and vice versa were observed over a long period, despite the fact that the patient was strictly isolated from other patients the whole time and never showed any signs of clinical diphtheria. In a paper on type changes in diphtheria, STRÖM (1948) has pointed out that this may mean an increase in time spent at the hospital. The possibilities of hospital

treatment must be improved so that fresh infection within the hospital itself is avoided. It would seem advisable to isolate all bacilli carriers from one another until the determination of virulence has been completed. It is advisable too to isolate the patients who are then found to have non-virulent bacilli from the others until they are fit for discharge according to the regulations in force. Definitely to exclude the possibility of re-infection of carriers who have received final treatment with penicillin, they too should be isolated from one another as soon as treatment is completed and until they are discharged.

Nasal carriers show a considerably greater resistance to treatment. This may be explained at least in part by the more favourable anatomical conditions for chronic infections offered by the nasal cavities. Quite obviously, a number of patients have been included who have had complications that may conceivably have adversely affected the therapeutic possibilities. Consequently, it is very important that the treatment is carried out in cooperation with a nose and throat specialist, so that it will be accompanied by suitable local therapy and disinfection.

Table 5

shows the 20 carriers unsuccessfully treated with 4—8 injections daily. There are only 8 with virulent bacilli and 5 of them have local complications.

	Number of Treatments			Positive cultures from	
	1	2	3	Throat and Nose	Throat
Virulent bacilli, no complications, 3 cases			3	3	
Virulent bacilli, Tonsillit. chron., 3 cases		2	1	3	
Virulent bacilli, Retropharyngit. atrophicans, 1 case			1	1	
Virulent bacilli, Palatoschisis, 1 case			1	1	
Non-virulent bacilli, 12 cases	7	5		9	3

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Table 5 gives a classification of the 20 patients who were not freed of bacilli in conjunction with treatment by 4—8 doses every 24 hours — in other words, with a treatment shown to be fairly effective. It will be seen that of the patients who must be included in the group »not free from bacilli», no less than 12 were carriers of non-virulent bacilli. On this account they were discharged with bacilli, in 7 cases as soon as after the first unsuccessful treatment. Of the remaining cases, 3 had chronic tonsillitis and became free of bacilli in conjunction with tonsillectomy.

That 4 negative cultures taken every third day after termination of treatment is not the same as definite freedom from bacilli has been pointed out earlier. In some cases the bacilli may appear later. Even if this is not so usual, it is necessary in certain cases to tighten up the requirements for discharge of patients. This is particularly the case with patients who, after being discharged, intend going to environments that are sensitive to infections, such as day homes, hospitals, schools etc., or those patients who have shown marked resistance to treatment. As soon as a patient with diphtheria bacilli arrives at the hospital, the home or the institution to which the patient will be going after discharge should be contacted and it should be suggested that all persons in this enviroment who are not vaccinated against diphtheria should be vaccinated. It is to late to think about this when the patient is about to be discharged.

The question of the extent to which the time carriers spend in the hospital may be shortened by penicillin treatment cannot be answered on the basis of this material. However, as a large percentage become free of bacilli in conjunction with the treatment, this must mean that the treatment has a definite value.

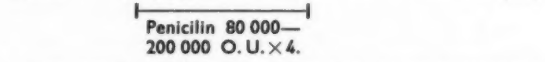

Diagram 3 illustrates the results of the bacteriological examinations in a successfully treated case. After 4 or 5 negative Clauberg and Löffler cultures and a negative Löffler culture on the last day, the patient was permitted to leave the hospital. Tests from throat and nose were taken every third day.

Diagram 3 shows the parenteral treatment which we consider gives the best terapeutic results at present. As pointed out earlier, the doses indicated must naturally be modified with respect to clinical effect. As a rule, the dose was increased 300 % if the first treatment was not effective. The diagram also shows the bacteriological requirements for the discharge of patients.

Summary

1. The investigation, which deals with 98 diphtheria carriers, has confirmed previous experience that parenteral treatment with penicillin is effective against diphtheria bacilli in vivo. Encouraging results were obtained with aerosol treatment.

2. 90 %—100 % of the carriers of pharynx bacilli became free from bacilli, but only slightly over 50 % of the nasal carriers, in conjunction with the treatmnet.

3. A suitable dose for adults seems to be 80 000—200 000 O. U. 4 times every 24 hours. The treatment should be extended over a sufficiently long period so that at least 3 negative Clauberg cultures in succession, taken every third day, may be obtained before it is terminated.

4. Positive cultures may appear some time after treatment has been stopped. At least 4 (in some cases 5) negative cultures in succession, taken every third day, should be obtained after treatment with penicillin before the patients are allowed to be discharged.

5. It is incorrect to exclude diphtheria following the obtaining of negative cultures during penicillin treatment. In cases where there is clinical suspicion of diphtheria, one must also take into account the fact that positive cultures may appear some time after the treatment has been stopped.

Résumé

1. Un examen comprenant 98 cas de porteur de diphtérie a confirmé les expériences acquises antérieurement, que le traitement parenteral par la pénicilline est effectif contre les bacilles de la diphtérie in vivo. Le traitement par l'aérosol a donné des résultats encourageants.

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2. Par suite du traitement, les porteurs de bacilles du pharynx ont été sans bacilles dans 90 à 100 % et les porteurs de bacilles du nez seulement dans un peu plus de 50 %.

3. La dose convenable pour les adultes semble être de 80 000—200 000 O. U., quatre fois toutes les 24 heures. Le traitement doit être continué durant une période assez longue pour obtenir, durant le traitement, au moins 3 cultures Clauberg négatives, successives, tous les 3 jours.

4. Des cultures positives peuvent se présenter quelque temps après la fin du traitement. Au moins 4 (dans certains cas 5) cultures négatives successives, tous les 3 jours, doivent être obtenues après le traitement par la pénicilline, avant qu'on permette au patient de quitter l'hôpital.

5. C'est une erreur que d'exclure la diphthérie par suite de cultures négatives durant le traitement par la pénicilline. En cas de soupçon clinique de diphthérie on doit tenir compte du fait que des cultures positives peuvent se présenter quelque temps après la fin du traitement.

Zusammenfassung

1. Die Untersuchung, welche 98 Diphtherieträger umfasst, hat die früheren Erfahrungen bestätigt, dass parenterale Penicillinbehandlung gegen Diphtheriebacillen in vivo wirksam ist. Ermunternde Resultate erhielt man mit Aerosolbehandlung.

2. Träger von Pharynx-bacillen wurden in 90—100 %, Träger von Nasenbacillen in nur etwas über 50 % in Zusammenhang mit der Behandlung bacillenfrei.

3. Eine geeignete Dosis für Erwachsene scheinen 80 000—200 000 O. E. viermal in je 24 Stunden zu sein. Die Behandlung soll sich über eine genügend lange Zeit erstrecken, so dass man mindestens 3 negative Claubergkulturen in einer Reihe, jeden 3. Tag entnommen, während der Behandlung erhalten soll.

4. Positive Kulturen können einige Zeit nach Behandlungsschluss auftreten. Wenigstens 4 (in manchen Fällen 5) negative Kulturen in einer Reihe, jeden 3. Tag entnommen, soll man nach der Penicillin-Behandlung erhalten, bevor der Patient ausgeschrieben werden darf.

5. Es ist falsch, bei einem während der Penicillinbehandlung erhaltenen Resultat von negativen Kulturen, Diphtherie auszuschliessen. In Fällen von klinischem Verdacht auf Diphtherie muss die Tatsache mit in Rechnung gezogen werden, dass positive Kulturen einige Zeit nach Behandlungsschluss auftreten können.

Resumen

1. El examen, que abarca 98 portadores de difteria, ha confirmado la experiencia anterior de que el tratamiento parentérico con penicilina es eficaz contra los bacilos de difteria in vivo. Se lograron resultados alentadores con el tratamiento aerosol.

2. Los portadores de bacilos de faringe resultaron libres de bacilos en 90—100 % y portadores de bacilos en la nariz sólo ligeramente arriba de 50 % en combinación con el tratamiento.

3. Una dosis conveniente para adultos parece ser de 80 000—200 000 O. U. cuatro veces cada 24 horas. Se debe extender el tratamiento por un período suficientemente largo, de manera que se puede obtener por 10 menos 3 cultivos negativos Clauberg en sucesión, sacados cada tres días, durante el curso del tratamiento.

4. Los cultivos positivos pueden aparecer algún tiempo después de que se ha terminado el tratamiento. Se deben obtener después del tratamiento del enfermo con penicilina por lo menos 4 (en algunos casos 5) cultivos negativos en sucesión, sacados cada tres días, antes de que se permita que el enfermo salga.

5. No es correcto excluir la difteria como un resultado de cultivos negativos durante el tratamiento con penicilina. En casos de sospecha clínica de difteria es necesario tomar en consideración también el hecho de que los cultivos positivos pueden aparecer algún tiempo después de terminado el tratamiento.

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FROM THE FLENSBURG CHILDREN'S HOSPITAL, MALMÖ.

On Prophylactic and Early Treatment of Infections in Newborn Infants, Especially the Premature

by

GRETA MUHL, M. D.

Although infantile mortality taken as a whole has undergone a gradual reduction during recent years, the mortality of the newborn, so-called neonatal mortality, has not merely failed to show any diminution but seems even to have increased in some places. It is no doubt because of the latter circumstance that infections in the new-born have recently been attracting greater interest.

Owing to their very low natural immunity, newborn infants, and particularly premature infants, are especially susceptible to infections which often become general because these children are unable to localize the trouble. Early diagnosis is difficult. The initial clinical symptoms are frequently very insignificant and not uncommonly entirely absent. The commonest are fever, which may or may not appear; loose stools, though these are also frequent among the newborn in other circumstances and hence are a commonplace symptom; cyanosis, which may be a symptom from the lungs but also appears in cerebral lesions and lethargy, which also occurs in the last-mentioned injuries and in severe cases of icterus, especially common among premature infants. Death often comes rather unexpectedly after sudden onsets of vomiting and diarrhoea, with or without lung changes.

The care of the newborn and particularly their protection against infections, cannot be regarded as satisfactory at those of our maternity hospitals — and they seem to be many — in where the children are nursed in large common wards by an un-

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trained and often — on account of the difficulties on the labour-market — insufficient staff. In these hospitals the principles adopted at modern children's hospitals of small wards and the least possible change of staff have not been applied. It is even to be feared that as far as infections are concerned, the conditions for the children are not so good as before, when the babies were attended together with their mothers in their homes or when the overcrowding at the maternity hospitals was not so great as it is now. At the Simpson Memorial Pavilion of the Edinburgh Royal Infirmary *Wallace* found during the years 1943—1946 that 25 % of all neonatal deaths among premature infants were due to infections which he considered avoidable to a great extent and when they occurred, usually due to incorrect or careless technique of care and management. Four-fifths of these infections were localized to the lungs. In order to provide against their recurrence, he commenced in 1947 prophylactic penicillin treatment of all premature children below 1600 g. in weight. This treatment was administered for the first 7 days, 6 000 units of the penicillin being given by mouth every third hour. PARMELEE (1947) reports 10 cases of sepsis among newborn infants and remarks on the frequency with which such infections occur.

At the Flensburg Children's Hospital these early infections used to be a rarity, but since 1944 we have had to treat numerous such cases (Tabl. 1). They have been especially frequent among premature infants (Table 2), but have also occured among the full-term children (Table 3). Since the year 1945 these children have usually been transferred from the Malmö Maternity Hospital to the Children's Hospital at the age of 5—6 days. Formerly they were sent over to the Children's Hospital earlier; during the period 1940—1944, for instance, fully half were transferred during the first 1—3 days of life, It is of interest that whereas most of the infections among our premature infants before 1944 were nosocomial, the majority occurring since 1944 have been neonatal. By »neonatal» infections we mean those in which symptoms have either already been exhibited on the children's admission to the hospital or have manifested themselves there by indubit-

Table 1

Infections Among Premature Infants.

Year	No. Infants Attended	Acute Infections		Number Deaths			Total Deaths	% Deaths
		Neo-natal	Noso-comial	Neo-natal	Noso-comial	Other Causes		
1940	40	1	12	1	3	3	7	17.5
1941	35	1	11	1	4	2	7	20
1942	39	2	7	—	3	1	4	10.3
1943	42	2	4	1	—	1	2	5
1944	58	14	8	11	1	2	14	25
1945	55	8	8	3	—	—	3	5.5
1946	63	9	2	2	1	—	3	4.7
1947	68	19	8	3	—	—	3	4.4
1948 1/1—30/4	23	7	3	1	—	—	1	4.3

able symptoms during the first few days; or infections in which from the outset the infants have been lethargic, fed badly and have often had to be fed through a stomach tube, or have had loose stools and fever or irregular temperature followed after 1—3 weeks by sudden and very unexpected attacks of vomiting and diarrhoea leading to death 2—3 days later or metastases such as osteomyelitis, arthritis, etc. Furthermore, while the mortality among the nosocomial cases is steadily declining — which may doubtless be attributed to the introduction of the new chemotherapeutic and antibiotic agents and perhaps also to the early treatment instituted of late years for children under observation at the Hospital —, the mortality among the premature now falls almost exclusively within the neonatal infections.

During the year 1944, 14 cases of neonatal infection occurred. 11 of these died, 6 with pulmonary changes, 3 with a toxicosis picture characterized by terminal vomiting and diarrhoea, and 2 in a sepsis-like state. The majority died soon after the appearance of clinical symptoms, death occurring at earliest on the eighth and never later than the twenty eighth day of life. The

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Table 2

Neonatal Infections Among Premature Infants.

Year	Diagnosis	No. Cases	Deaths	% Deaths
1944	Bronchitis, Bronchopneum., Capill. Br.	8	6	
	Entero-colitis Ac.	4	3	
	Sepsis ?	2	2	
		14	11	78.5
1945	Bronchitis, Bronchopneum., Capill. Br.	4	2	
	Entero-colitis Ac.	3	1	
	Omphalitis	1	—	
		8	3	37.5
1946	Bronchitis, Bronchopneum., Capill. Br.	3	1	
	Entero-colitis Ac.	3	1	
	Sepsis and Osteomyelitis	1	—	
	Omphalitis	2	—	
		9	2	22.2
1947	Bronchitis, Bronchopneum., Capill. Br.	7	—	
	Pneumonia Crouposa	1	1	
	Entero-colitis	2	1	
	Sepsis and Osteomyelitis	1	—	
	Cryptogenic Infection	2	1	
	Omphalitis	4	—	
	Erysipelas	1	—	
	Arthritis Septica	1	—	
		19	3	15.8
1948	Bronchitis, Bronchopneum., Capill. Br.	5	—	
1/1–30/4	Cryptogenic Infection	2	1	
		7	1	14.3

Table 3

Neonatal Infections Among Full-Term Infants.

Year	Diagnosis	No. Cases	Deaths
1947	Bronchitis, Bronchopneumonia	1	1
	Entero-colitis Ac.	1	—
	Cryptogenic Infection	1	—
	Omphalitis	3	—
		6	1
1948 1/1—30/4	Bronchitis, Bronchopneumonia	1	—
	Sepsis	1	—
	Entero-colitis	1	—
	Omphalitis Ac. + Entero-colitis Ac.	1	—
		4	—

cases were distributed fairly evenly over the year, with a concentration during early summer and again during Nov.—Dec. with an extension into January of the following year. In July—August 1944 an epidemic of pemphigus broke out in the Maternity Department, staphylococcus aureus being considered the causal agent. The 1944 diseases among the newborn were also such as may be produced by this bacterium. Especially the enteral infections — which in their clinical course resemble the acute malignant gastro-enteritis that has appeared of recent years, though the latter may be excluded here on account of the absence of epidemic appearance — may, as we know, be generated by staphylococcus aureus, as *Cummings* has recently shown. Our treatment, consisting of administration of fluids, stimulants and sulfanilamide drugs on the appearance of the symptoms, was in most of the cases without effect, possibly because it came too late.

During the following years the neonatal infections continued, with a diminution during 1945 and 1946 but a distinct rise during the 2 last years (Table 2). For the time being external conditions made it impossible for us to institute an effective prophylaxis to reduce the infections, but it soon became very necessary at

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least to try to diminish the mortality. It was manifest that if treatment was not introduced until distinct symptoms of infection appeared, then that treatment was in a number of cases ineffective, and this continued to hold true even after penicillin became available in 1946. In several of the cases that had a rapid lethal termination we had found high leuocyte values, and we began to test the possibility of arriving at earlier diagnosis and treatment by means of blood examination. As is known, the white bloodcorpuscles react early to infections, and this fact ought to be of use especially in the case of premature children, in whom other symptoms are frequently long delayed or difficult to interpret.

The leucocytic conditions in healthy premature infants during the neonatal period are known from the investigations of, among others, LICHTENSTEIN and MAGNUSSON in Sweden. The latter examined 112 infants. His findings show that during the neonatal period the number of white bloodcorpuscles only slightly exceeds 12 000 on any day. Numerous determinations made on a large number of healthy premature children at the Flensburg Children's Hospital, especially during the last year, are in entire agreement with these values.

Upon examining children undoubtedly suffering from infections, we have found in the majority of cases leucocytosis with values up to 15 000—45 000 and a marked increase in the polymorphonuclear cells. In a few cases leucopenia has occurred, at least in the beginning. The stabs have often increased very markedly and in some cases early severe anemia has developed. Gradually we commenced to make more and more blood counts for our newborn infants, and these are now being made for all. In many cases this procedure has disclosed leucocytosis before other symptoms of infection could be established and thus enabled us to start treatment early. In not so few cases of lethargic children or of children with dyspeptic symptoms, these blood examinations have confirmed our suspicion that an infection was present. On the other hand, we have not derived any benefit from determining the mean sedimentation rate, which rather seldom reacts to infections at these ages.

When an increase in the number of white bloodcorpuscles is being evaluated for differential diagnostic purposes, it should be taken into account that the number may be increased, though not much, in haemorrhages. Regard should also be paid to the fact that even mild infections may react with elevated values. Such is the case with the rather common acute forms of conjunctivitis, values up to 20 000 being encountered here at times, though they are usually lower. Rhinitis, which as a matter of fact rarely occurs at this age, sometimes gives higher values, and when this is the case in premature infants I consider it desirable to institute therapy, as the infection has a tendency to spread rapidly to the lungs.

Finding that the risk of neonatal infections was increasing rather than decreasing among our premature infants, we have adopted the following procedure during the last year. If on admission to the hospital the children have leucocytosis with values between 15 000 and 20 000 or higher, and if they are poor feeders or lethargic without there being a suspicion of cerebral haemorrhage, or if they have loose stools, penicillin treatment is immediately commenced, with 5 000—10 000 units 8 times per 24 hours. Of late we have also employed three doses of 30 000 units each daily. If the stools have been very disagreeable, recourse has also been had to sulfanilamide drugs in the form of sulfaguanidine or sulfthalyl. The same treatment is employed if there are pulmonary changes or umbilical infection. If leucocytosis is present but there are no other symptoms, expectant treatment is resorted to, the blood values being followed and the child carefully examined every day and regarded as in the danger zone. It then happens not infrequently that after a day or two pathological changes are found in the lungs, changes which often come early. These changes, which are generally considered to indicate a very poor prognosis, have turned out better since we started this treatment. It is probable that they would not have been diagnosed so early if we had not known of these blood values, for in the case of these little children it takes rather a long time for lung changes to give clinical symptoms in the form of coughs, dyspnoea and cyanosis, and when these appear the best time for treatment is doubtless already past.

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If a real leucocytosis persists for several days without any local symptoms appearing, treatment is also commenced even if the patient is unaffected. Not until after several days to weeks has osteomyelitis, omphalitis, arthritis or pneumonia then appeared, and thanks to the blood examinations treatment in these cases could be started much earlier. In some of these cases a septic condition has gradually developed without local symptoms ever having occurred. Table 4 presents some cases treated thus early.

In September 1947 a slight epidemic of neonatal infections occurred in Ward A of the Maternity Department of the Malmö General Hospital. This has been described by Muhl. As the risk of infection in the Maternity Department was evidently great, at any rate at times, and the premature children were not transferred to the Children's Hospital until their fifth or sixth day of life, we began to consider prophylactic treatment of these during the period while they were still in the Maternity Department, just such a procedure as we later learned Wallace had inaugurated in Edinburgh. However, as it was deemed inadvisable to handle these delicate infants overmuch, and as the staff of the Maternity Department was fully engaged, we confined our attentions to the children who could be regarded as most threatened, *viz.* those injured during delivery, those who had undergone long deliveries, those who aspirated or were asphyctic and in general all who appeared to be bad cases in any way, treating them prophylactically with penicillin and sometimes also with sulfanilamides. The time has as yet been too short to permit assessment of the benefit derived from this treatment, other than to say that the prophylactic measures in the Maternity Department may have contributed to improving the results of our treatment of those who on admission to our own department were infected and had received such pre-treatment.

In Table 2 a list is given of the infections which occured among premature infants during the years 1944—30/4 1948, and in Table 3 some cases are submitted of infected full-term children during the period 1/1 1947—30/4 1948. The pulmonary infections are the most common, as seems to be the general rule.

Table 4

Cases Treated Prophylactically or Early.

No.	Birth Wt.	Age in Days	Clinical Symptoms	White Blood Corp.		M.S.R.	Diagnosis	Treatment	Condition on Disch.
				Total No.	Polymorphonuclear				
418/46	2140	9	Leucocytosis	18 800			Periumbil.	S	
		12	»	18 800	10 800		phlegmon		
		15	Tense abd. Large abd. veins	33 000	26 200				
		17	Periumbil. phlegmon	30 800	27 000			P	Well
904/46	1590	6	Remittent fever and	22 400			Crypto-	S	
		12	oscil. temp. 2 weeks	35 000			genic inf.	P	
		13		19 700					
		32		21 400					Well
653/47	1900	5	Very lethargic.	24 400	14 000	1—2	Crypto-		
		7	Tube-fed. Oscil. temp.	25 200	19 400		genic inf.	P	
		14		19 500	13 000				
		18		9 800	5 400				Well
675/47	2160	11	Exuding navel. Pale	19 000	12 200	1—2			
		12	and debilitated						
		17	Osteomyel. Abdom.	18 000	12 100	2.5—6	Sepsis	P	
			tense with l. veins						Well
871/47	2160	7	Offensive watery stools.	13 000	5 000	2—4	Umbil. inf.	P at	
		8	Exuding navel. Obvi-	25 000	14 000		+ Entero-	Mat.	
		15	ously lethargic.	16 200	8 200		colitis	S	Well
882/47	1750	8	Vomiting, diarrhoea,	16 000	10 200		Sepsis-	S+	
		9	cyanosis. Lethargic.				like con-	P	
		21	Tube-fed	20 000	12 800		dition		Well
795/48	1750	8	Cyanotic, lethargic,	13 000	6 800			P	
			tube-fed						
		9	Bronchitis persisting			1—2	Bronchitis		
			4 weeks						Well
851/47	1250	7	Wt. 970 g. Whining	20 200	14 300	1—2		P	
		8	child that moans faintly	24 000	18 200				
		11	Vomiting, loose stools.	26 000	16 400	2.5—5	Crypto-	S	
		22	Sudden exitus.				genic inf.		
			Autopsy find neg.						Dead
17/48	2020	13	Tube-fed. S.R. long	18 400	11 600	32—38	Crypto-	P	
		14	time high, early severe	24 600	19 800		genic inf.		
		19	anaemia	13 000	4 600	20—22			Well

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Then come the enteral infections, next general infections with or without local symptoms, and following these the umbilical infections. As bacteriological tests were not made on this material, I have used the term »sepsis» only for cases in which metastases occurred or the patho-anatomical diagnosis was beyond doubt, as well as in one case, of a full-term child in which the simultaneous occurrence of fever, cutaneous and mucosal haemorrhages, and leucocytosis could be considered as verifying the diagnosis. The mortality has declined from 78.5 % of the infected in 1944 to 14.3 % during the period 1/1—30/4, 1948. Since the prophylactic treatment of specially threatened infants was inaugurated in the Maternity Department, where since the autumn of 1947 the children have been attended by the medical staff of the Children's Hospital 13 cases of neonatal infections have occurred in the Children's Hospital, 8 of which had been prophylactically treated with penicillin at the Maternity. All of the 8 so treated survived. Of the 5 that were not pre-treated, 2, with birth-weight of 1 250 and 1 520 gms., died. They had been unaffected at the Maternity and therefore had not received any treatment there. On admission to the Children's Hospital at the age of 7 days both had leucocytosis and 1 rhonchus of the lungs and a high M. S. R. If prophylactic treatment had been started in these cases, it is possible that the issue whould have been different. With these 2 cases in mind it would seem advisable always to have recourse to prophylactic treatment of very small premature infants if there is any risk of their being infected, even if they do not appear to be affected.

In the case of the nosocomial infections, which unfortunately cannot be entirely avoided at a children's hospital, we have also instituted early treatment. The infections in question here are almost exclusively those which affect the upper respiratory tract. At a children's hospital, where attention is directed toward quick recognition of the first symptoms, treatment can commence early, and according to our experience these cases are now turning out very well. Since 1944 we have had only 2 deaths in our hospital from nosocomial infection among the prematures.

The aforementioned slight epidemic in September 1947 gave

rise on the one hand to our inauguration of prophylactic penicillin treatment in the Maternity Department of the infants most threatened and, on the other hand, to a bacteriological investigation in Ward A by Dr. Winblad and his assistants. During the period 1/12 1947—28/2 1948 the noses and throats of all the children were examined every other day during their stay in the ward, which as a rule lasted for 7 days after their birth. These examinations of 127 children which have not yet been published but which Dr. Winblad has given me permission to cite, showed that 88 % of all the children aged 3 to 5 days examined had staphylococcus aureus in the nasal mucous membrane in such abundance that it could be denoted a pure culture. This bacillus was not found in any high percentage among the hospital staff, unlike the state of affairs in an epidemic described by me in which 5 healthy carriers with an abundant growth of this bacterium were found and unlike what Winblad and other authors have found in epidemics of pemphigus neonatorum.

These investigations show good agreement with, for example those of TORREY and REESE.

Of all the children with staphylococci, however, only a few fall ill. Apparently this does not occur unless some further factor is added. What this is is as yet completely unknown. It may be conjectured that a virus is added as a complication or that the virulence of the bacteria present becomes intensified.

Under any circumstances when staphylococcus aureus, which is one of the commonest bacteria to cause infections in infants, occurs to the extent of 88 % among the newborn in a maternity ward, it must be regarded as an element of danger that may give rise to a piling up of infections such as that which occurred in Malmö in September 1947. Even if there are no epidemics, the number infected there — if account is taken only of those infants transferred to the Flensburg Children's Hospital during the last few years — is too high, especially if we take into consideration the fact that these infections could have been avoidbale.

By means of ultra-violet radiation of the rooms occupied by the newborn TORREY and REESE have succeeded to a certain

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extent in reducing the number of staphylococci in the children's rhinopharyngeal flora. Treatment of this kind may, of course, be attempted. However, since general experience has shown that the hospital staff has been the source of infection when epidemics have occurred, our attention must in the first place be directed to this aspect of the question. The most important step would therefore be to provide small wards for the premature infants and, above all, a trained permanent staff, an end that at present lies in the realm of pious wishes but which must nevertheless be pursued.

Summary

Neonatal infections among children transferred from the Maternity Department of the Malmö General Hospital to the Flensburg Children's Hospital during the last 4—5 years have increased considerably, doubtless because of difficulties in affording ward accommodation and procuring a suitable nursing staff.

To neutralize to some extent the dangers that threaten the newborn, we at the Children's Hospital have directed our efforts towards early diagnosis and treatment of these infections. We have found determination of the white blood corpuscles of benefit, inasmuch as these, especially the polymorphonuclear cells, often increase before clinical symptoms appear. In many cases leucocyte counts have enabled us to commence treatment earlier than would have been possible otherwise.

However, since premature and diseased children are usually not transferred to the Children's Hospital until the 5th—7th day of life, for the past 9 months we have conducted prophylactic treatment of infants especially disposed to infections (viz. the asphytic, those who aspirate and those lethargic after cerebral injuries or other parturient lesions) in the Maternity Department. It is these children who are prone to contract the early affections of the lungs which in this as well as other materials appear to dominate among the neonatal infections. This category of specially threatened children should also embrace the very small infants with birthweights under 1 500 g., as these have proved to belong to the specially delicate class.

The results obtained have been encouraging. The mortality among the infected has dropped from 78.5 % during 1944 to 37.5 %, 22.2 %, 15.8 % and 14.3 %, respectively, during the subsequent years.

Résumé

Le nombre des infections néo-natales parmi les enfants transférés de la section de l'Hopital Général de Malmö à l'Hopital d'enfants de Flensburg a augmenté considérablement, durant ces 4—5 dernières années; sans doute, à cause des difficultés de se procurer des locaux appropriés et de trouver un assez grand nombre d'infirmières capables.

Pour neutraliser dans une certaine mesure, le danger qui menace les nouveaux-né, nous avons, à l'Hopital d'enfants, dirigé nos efforts vers un diagnostic et un traitement prompts de ces infections. Nous avons trouvé utile et avantageux de faire la détermination des globules du sang, d'autant plus que ceux-ci, particulièrement les cellules polymorphonucléaires, se multiplient souvent avant l'apparition des symptômes cliniques. Dans bien des cas, le nombre des leucocytes nous a permis de commencer le traitement plus tôt qu'il n'eût été possible autrement.

Cependant, depuis que les enfants prématurés et les malades ne sont habituellement pas transférés à l'Hopital d'enfants avant le 5e—7e jour de leur vie, les 9 mois passés nous avons établi à la section de maternité, un traitement prophylactique pour les enfants spécialement receptifs aux infections, (tels que les enfants atteints d'asphyxie, ceux qui aspirent ainsi que ceux tombés en léthargie après une lésion cérébrale ou autre lésion de naissance). Ce sont les enfants qui ont tendance à contracter les »primo-affections» des poumons, qui, dans cette matière aussi bien que dans d'autres, semblent dominer parmi les infections néo-natales. Cette catégorie d'enfants spécialement menacés comprendrait aussi les enfants très petits: d'un poids de naissance inférieur à 1 500 gr. puisqu'ils se sont montré appartenir à la classe d'enfants particulièrement délicats.

Les résultats obtenus ont été encourageants. La mortalité

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parmi les enfants infectés a diminué de 78,5 % en 1944 à 37,5 %, et respectivement à 22,2 %, 15,3 % et 14,3 %, durant les années suivantes.

Zusammenfassung

Die Neugeborenen-Infektionen unter den von der Mütter-Abteilung des Malmöer allgem. Krankenhauses in das Flensburger Kinderspital überführten Kindern haben während der letzten 4—5 Jahre beträchtlich zugenommen, ohne Zweifel wegen der Schwierigkeiten mit der Hospitalization und der Verschaffung des geeigneten Pflegepersonales.

Um dem weiteren Zunehmen der die Kinder bedrohenden Gefahren entgegenzutreten, haben wir am Kinderspital unsere Bemühungen auf frühzeitige Diagnose und Behandlung dieser Infektionen gerichtet. Wir fanden, dass die Bestimmung der weissen Blutkörperchen von Nutzen ist, da diese, besonders die polynukleären Zellen, oft zunehmen, bevor klinische Symptome auftreten. In manchen Fällen haben die Leukozythenwerte uns zu einem zeitigeren Behandlungsbeginn verholfen, als es sonst möglich gewesen wäre.

Da die praematuren und kranken Kinder gewöhnlich nicht vor dem 5.—7. Lebenstag ins Kinderspital eingebracht werden, haben wir während der letzten 9 Monate prophylaktische Behandlung der besonders für Infektionen disponierten Kinder (asphyktische; solche, die aspiriert hatten u. solche, die nach cerebralen Schädigungen oder anderen Geburtstraumen lethargisch waren) in der Mütterabteilung durchgeführt. Diese Kinder neigen zu frühzeitigen Lungenaffektionen, welche sowohl bei diesen Kindern, als auch bei anderem Material unter den Neugeborenen-Infektionen vorzuherrschen scheinen. Diese Kategorie der speziell zu behandelnden Kinder soll auch die sehr schwachen Kinder mit einem Geburtsgewicht unter 1 500 g umfassen, da auch diese zu der besonders empfindlichen Klasse gehören.

Die erhaltenen Resultate waren ermutigend. Die Mortalität bei den Infizierten sank von 78,5 % im Jahre 1944 auf 37,5 % bzw. 22,2 %, 15,8 % und 14,3 % während der folgenden Jahre.

Resumen

Han crecido considerablemente las infecciones neonatales entre niños transferidos de la Maternidad del Hospital General de Malmö al Hospital de Niños de Flensburg durante los últimos 4—5 años, indudablemente a causa de las dificultades de poder proveer cuadras de acomodación y de obtener personal conveniente de enfermeras.

A fin de neutralizar en algún grado los peligros que amenazan al recién nacido, en el Hospital de Niños hemos dirigido nuestros esfuerzos hacia diagnosis y tratamiento adelantado de estas infecciones. Hemos encontrado útil la determinación de los corpúsculos blancos de la sangre, puesto que éstos, especialmente las células polimorfonucleares, muchas veces crecen antes de que los síntomas clínicos aparecen. En muchos casos los cómputos de leucocitos nos han permitido empezar el tratamiento antes de lo que hubiera sido posible de otra manera.

Sin embargo, en vista de que los niños prematuros y enfermos no se trasfieren generalmente al Hospital de los Niños hasta el quinto — séptimo día de vida, durante los últimos 9 meses, hemos practicado tratamiento profiláctico de niños especialmente dispuestos a infecciones (es decir, los asfictícos, los que aspiran y los letárgicos después de daños del cerebro u otras lesiones parturientes) en la Maternidad. Son estos niños los que tienen inclinación a contraer afecciones anticipadas de los pulmones, las cuales en este caso, así como en otros, parecen dominar entre las infecciones neonatales. Esta categoría de niños especialmente amenazados debe abarcar también los bebés muy chicos con pesos de nacimiento de menos de 1 500 gramos, en vista de que se ha probado que estos niños pertenecen a la clase especialmente delicada.

Los resultados que se han logrado son alentadores. La mortalidad entre los infectados ha bajado desde 78,5 % durante 1944 a 37,5 %, 22,2 %, 15,8 % y 14,3 %, respectivamente, durante los años subsiguientes.

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Airborne Infections

IV. The Control of Dustborne Streptococcal Infections in Children's Wards

by

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In an earlier investigation (8) nosocomial (hospital cross-) infections were studied in connection with the presence of haemolytic streptococci in a hospital for children. The infection was mainly spread by so-called dangerous carriers. The present paper is a report of a further study of the importance of such carriers. Tests were made with one of the prophylactic measures used in England and America, i. e., oiling of textiles and floors.

The first studies in this field were made in England by VAN DEN ENDE, LUSH, and EDWARD (21). They demonstrated that the number of bacteria that are stirred into the air when a floor is swept is 89 % less when a floor has been treated with oil emulsion than when it is untreated. THOMAS obtained the same results as did ROBERTSON and co-workers (13, 15, 16).

Only a few reports have hitherto been published on the effect of an oiled floor on the occurrence of respiratory tract infections. FEASBY and BYNOE (6) found that a considerable reduction of such infections resulted from the oiling of floors combined with satisfactory ventilation. ANDERSON, BUCHANAN, and MACPARTLAND (1) found in an investigation on military personnel that there was a decrease from 38 respiratory tract infections per 1000 men per week in the controls to 7 cases per 1000 men per week in the oil-treated unit. Later control studies by WRIGHT, CRUICK-

SHANK, and GUNN (22) and by SCHECHMEISTER and GREENSPAN (14) were, however, unable to show that oiling of the floors alone decreased the number of respiratory tract infections. The procedure was therefore relatively soon extended to include the oiling of textiles, blankets, sheets etc., which were found to be important sources of infection. Again the first experiments were made in England, by ANDREWES, VAN DEN ENDE, LUSH, SPOONER (2, 17, 18, 19, 20), etc. The first practical method was introduced by HARWOOD, POWNEY, and EDWARDS (7). It was later improved by ROBERTSON *and co-workers* (10, 12) in America and finally by SCHECHMEISTER and GREENSPAN (14).

A number of studies have shown that the addition of 2.5—6.5 % oil to textiles is sufficient to reduce the number of bacteria released by beating by 90—95 %. Studies have been made on the effect of combined oiling of the floors and textiles on the number of secondary infections in hospitals and barracks. By oiling the floor and bedclothes, WRIGHT, CRUICKSHANK, and GUNN (22) reduced the number of secondary streptococcal infections in a morbilli ward from 58.1 to 18.6 %. The incidence of secondary infections in the control ward during a corresponding period was 53.3 and 73.3 % respectively. The Commission on Airborne Infections (4) in the U. S. A. tested the method in military barracks and found a decrease of 24 % in the upper respiratory tract infections in the oil-treated units.

Nevertheless, reports that no decrease in nosocomial infections follows oil treatment have been published during the past year. BEGG, SMELLIE, and WRIGHT (3) found 12.4 % of such infections in 186 patients in an unoiled ward and 20.5 % in 190 patients in an oiled department. Two large American control investigations (5, 14) on military material also gave mainly negative results. In one, a slight decrease in the number of respiratory tract infections was found during a period with a low frequency of infections but no decrease during periods of epidemics. The other showed varying incidences during different periods and no significant difference was found. The value of the oil impregnation of blankets and bedclothes and oiling of floors must therefore be considered as incompletely established at present.

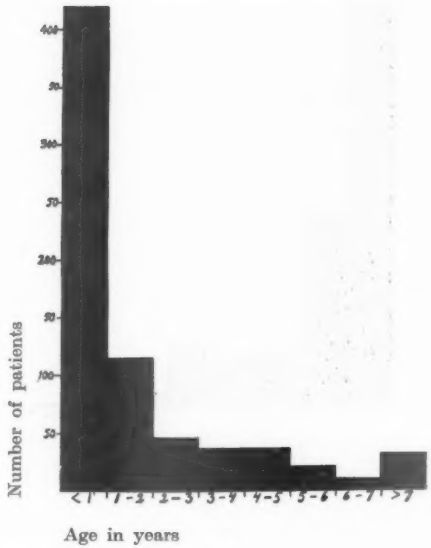

Fig 1.

In several of the above investigations the experimental conditions were not fully comparable in the treated and the control groups. Nor were any attempts made to explain the varying results obtained.

Scope of the Investigation

The period of investigation covered the period from September 3, 1946 — April 21, 1947. The hospital was the same as in the earlier study, i. e. the Sachs Hospital for Children, Stockholm. The two units in which the tests were made were entirely uniform as regards planning and routine. Admission took place on alternate days. In one unit (Unit II) the floor and textiles were treated with oil. The other (Unit I) served as a control.

The distribution of the patients according to age is indicated in Fig. 1.

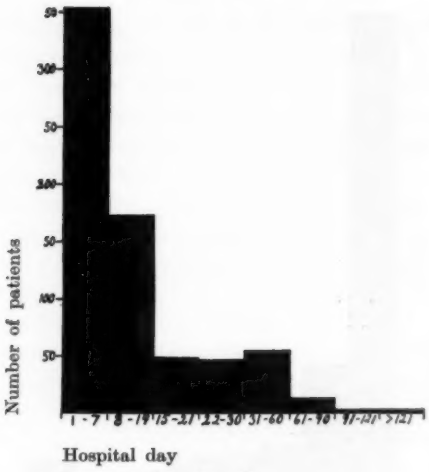

Fig. 2.

It will be seen from the table that the majority of patients were infants and children aged from 1—3 years and, to a certain extent, up to the age of 6—7 years.

In the majority of instances the children were admitted through the outpatient department of the hospital or directly from various parts of the town and only in a few instances from the country. The material can thus be considered as representive of that in a children's clinic. The average duration of hospitalization is shown in Fig. 2.

The Methods

The appearance of the hospital units, the routine with regard to the risk of infection, and the clinical, bacteriological, and serological tests have been described earlier (8, 9). No details will, therefore, be presented here. The bacteriological tests were focussed particularly on the presence of β-haemolytic streptococci. Serological typing of the streptococci was performed as completely as possible by Dr. P. Hedlund at the State Bacteriological Laboratory.

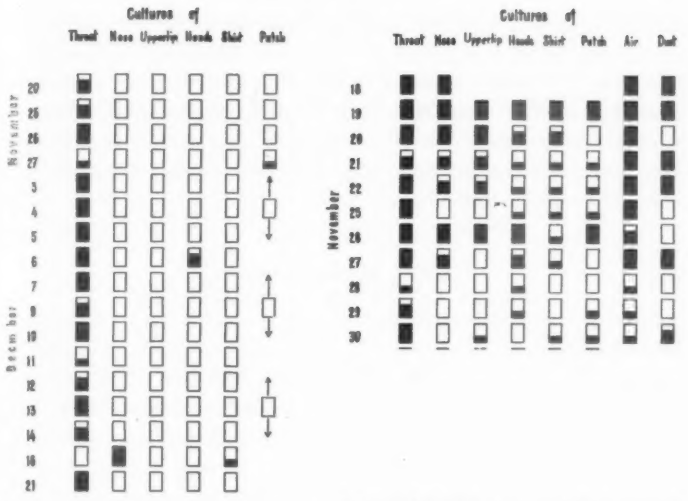

Fig. 3. Example of occurrence of β-haemolytic streptococci in person of spreading type compared with non-spreader of bacteria.

A short account is given in the following of the special method used for the detection of carriers and of that used in oiling the floors and textiles.

Technique for the Detection of Carriers

The test was made by rubbing a swab dipped in broth on the upper lip immediately below the nose, on the dorsal aspect of the hands, and on the shirt at the level of the mid-chest. For comparison a culture was taken from a piece of flannel that had been sewn to the outside of the shirt for 24 hours.

In addition to these direct tests, the effect of spreading was studied by means of analyses of the air with the slit sampler and sedimentation plates as well as by analysis of the dust. Fig. 3 shows an example of how this method functions.

It will be seen from the figure that in one case (the columns on the right) abundant streptococci were found in cultures from the nose and throat as well as from the upper lip, the hands,

and clothes, with spreading of the bacteria to the air and dust. This is thus characteristic of the spreader of infection. In another case (the columns on the left) the streptococci were almost as abundant in the throat but were present only in small numbers in other specimens. This is an example of a carrier of infection who does not spread it. Every case with streptococci was examined according to the foregoing.

Oiling of the Floors

The floors were covered with linoleum. Before oiling they were washed with green soap-and hot water and thereafter allowed to dry for 16—24 hours. The oil, of the spindle-oil type, fulfilled the conditions stated by ROBERTSON *and co-workers* (10 a). It was spread with large mops in order to cover the floor as rapidly as possible. There was a certain risk of slipping during the first hours, but later the oil made very little difference in this respect. The floors were oiled once more after two weeks and again after a further two weeks and subsequently every fifth week. If for any reason it was necessary to wash the floor during the interval, oil was applied after washing. The oiled floors were swept with brooms but not polished. The quantity of oil required must be tested for each floor with a view to its covering and the wear to which it is exposed. The quantity may vary between 50 and 200 g per square meter of floor. The smell of oil, which was at first somewhat disagreeable, was removed by the addition of a small amount of aromatic oil.

Oiling of the Textiles

The textiles were oiled with the method described by ROBERTSON *and co-workers* (10, 12) with T 13 (Triton oil emulsion). Blankets, sheets, pillow-cases, night-dresses, pyjamas, etc. were treated. The amount of oil that should be present in the textiles after treatment is between 3—5 %, calculated per kg dry weight. In the present experiments it was found on determination of the amount of oil absorbed by the textiles that it was at times 0.5—

1 % lower than that given by the aforementioned authors. It was not possible to ascertain the reason for this difference. Bacteriological tests on the dustholding properties nevertheless gave results that are stated by the aforementioned authors as satisfactory.

Oiling was performed in the laundry of the hospital and was found to be easily introduced into the ordinary routine. No disadvantages were observed.

Occurrence of Streptococci in Patients

Tab. 1 shows the results of the tests for the presence of haemolytic streptococci in patients and personnel.

Method	Experimental Material	Number	Acute Streptococcal Infections			
			No Nosocomial Infection		Nosocomial Infection	
			No.	Percentage	No.	Percentage
Oiled Unit	Patients	304	29	9.5 %	15	4.9 %
	Personnel	59	3	5 %	17	28.8 %
Unoiled Unit	Patients	276	26	9.4 %	8	2.9 %
	Personnel	68	9	13.2 %	17	25 %

Tab. 1.

Unit I (control). Cultures from the throat or nose showed haemolytic streptococci in 34 of the 276 children. Streptococci were found on admission in 26 of these children, whereas 8 became infected during their stay in hospital. These 8 children, i. e. 2.9 % of all the patients in the unit, represent the number of nosocomial streptococcal infections. In a further two instances, in which streptococci were present on admission, these changed in type during hospitalization, i. e. from Type 14 to Type 4 and from Type 12 to Type 23, respectively. In no case was the change in

type accompanied by any fresh pathological symptoms. Since the significance of the change in type in healthy carriers is uncertain, these two cases were not included in the nosocomial infections. One of the children suffering from nosocomial infection, whose stay in hospital was long, was infected by streptococci on 3 separate occasions. In those instances in which the streptococci were typed, all were found to belong to Lancefield's Group A, with the exception of one belonging to Group B. The most common types were 4, 6, 11, 12, 14, 19, 23, and 25. No particular type predominated. The majority of cases were clinically mild.

Unit II (*oiled*). Haemolytic streptococci were isolated from 44 of the 304 children. These were found on admission in 29 of the patients, whereas 15 were infected during their stay in hospital. There was thus an incidence of 4.9 % nosocomial infections in the oiled unit. One of the nosocomially infected children (Case 1?) was admitted to hospital for an infected eczema caused by streptococci Type 24. During hospitalization a throat infection developed caused by streptococci Type 5. There was also one instance of a change in type from Type 11 to 4 in one primarily infected child. Since this was not accompanied by any fresh clinical signs of infection for the reasons mentioned in the foregoing, this case was not included in the nosocomial infections.

In those cases that were typed, the majority belonged to Group A, but a few cases belonging to Group B and H also occurred. The most common types were 4, 5, 12, 14, and 24. Type 14 gave rise to a minor epidemic. Case 13, who was infected with this type of streptococci and who was a dangerous carrier, was the cause of 4 secondary cases during the first week he was treated in the unit.

Occurrence of Streptococci in the Medial Staff

Streptococci were isolated from 6 of the 9 physicians on duty. In no case were streptococci found at the beginning of their appointment but all became infected at the hospital. Two were infected by Case 13 and one was a carrier of streptococci for over 5 months, while another, who was infected with streptococci of

Type 24, was a carrier for over 4 months. Streptococci were isolated on single occasions from two more doctors. All cases with the exception of one were only throat carriers and did not spread the infection. One also had positive cultures from the nose for a few days and was found to be a spreader during that time. It was not possible to show that any of the doctors gave rise to secondary cases. The two who did not become infected with streptococci served at the hospital for only one and two months, respectively, whereas the appointments of the others varied between 5 and 7 months.

Occurrence of Streptococci in the Nursing Staff

Unoiled Unit. Sixty eight nurses and wet-nurses were on duty in this unit. No streptococci were isolated from 43 of them. Some of these nurses, however, were on duty at the hospital for short periods only and in 12 instances only one or two tests were made. Streptococci were isolated from 23 nurses. Nine of them were already infected on taking up their appointments and 14 were infected at the hospital. In 5 of the 23 streptococci were found on one occasion only, whereas in all the others they were repeatedly isolated.

The majority of the personnel were only throat carrieres. In 4 cases streptococci were also isolated from the nose, in two of them only on one or two occasions but more regularly in the two others. One of these carriers was a markedly dangerous carrier whereas the other only spread bacteria in the surroundings on a few occasions. Plentiful streptococci were isolated from the air and the dust during the time that the nurse who was a dangerous carrier was on duty in the unit. One of the patients nursed by her contracted acute pharyngitis, and streptococci were then isolated.

Oiled unit. Fifty-nine nurses and wet-nurses were on duty in this unit. No streptococci were shown in 42 of them. Nevertheless, as in Unit I, these nurses often only held shorttime appointments. One or two tests only were made in 14 instances. Streptococci were isolated in 17 cases, of which only 3 were carriers when

they took up their appointments. One of these primary carriers was free from streptococci for over a month but later developed acute tonsillitis from which abundant streptococci were isolated. She was then a carrier for 3 months. She could thus be considered as not only primarily but also nosocomially infected.

Among the 14 cases who were carriers during the period they were on duty, streptococci were found on only a few occasions in 7 instances, but more regularly, often for several months, in the remainder. In the majority only the throat specimens were positive but streptococci were isolated from the nose as well in 4 instances. In one of them the specimen was positive on one occasion only and in the others for from 1—3 weeks. These 3 were shown to spread the infection. One, a wet-nurse, presumably infected an infant, Case 30, during the time that positive cultures were found in the nose. She had earlier been a carrier of streptococci in the throat for about 3 months but was not a dangerous carrier during that time. No source of infection could be traced to either of the two other dangerous carriers nor to the remainder of the personnel.

Case Reports

A number of cases found in the present study are excellent examples of various types of spreaders and carriers of infection. Short case histories are therefore given in the folloring.

Case 13. A boy aged 4 $^1/_2$ years. He became ill one week before admission with fever and sore throat. It is of interest to note that a neighbour's child who had played with the patient the day before the latter became ill had been ill with fever and sore throat one week earlier. The mother of the patient became ill with throat trouble at the same time as her child.

After a few days the temperature was 38.6° C and he suffered from nausea, vomiting, and abdominal pains. Simultaneously, small reddish eruptions appeared on the trunk and extremities, particularly on the arms and legs, which the patient scratched owing to the itching. The appearance and extent of the eruption will be seen in Fig. 4.

Fig. 4.

The patient was admitted to hospital on Oct. 15, 1946.

Condition on Admission General condition very good, temperature 37.8° C. The clinical picture was dominated by the skin eruption in the form of small haemorrhagic papules. In a number of them there were vesicles whose content was partly clear and partly cloudy. The only other clinical symptom was a reddening of the throat and enlarged tonsils. Leukocytes 13 000; microsedimentation rate 36 mm/hr; antistreptolysin titer (9 days after admission) 800 U/ml.

Bacteriological cultures from the throat and vesicles revealed abundant haemolytic streptococci of Group A, Type 14. The child was also found to be a spreader of infection. Routine control of the dust and air showed numerous streptococci only 24 hours after admission of the patient, not only in the ward in which he was treated but in all the other wards, corridors, and examination rooms.

The skin symptoms disappeared rapidly in connection with treatment, while the leukocyte count fell to 7000 and the micro-

sedimentation rate to 22 mm/hr. One week after admission, administration of penicillin and Elkosin (6-sulphanil-amido-2, 4-dimethyl-pyrimidine) was started. No streptococci could be isolated from the throat or vesicles after 5 days' treatment. The child was discharged after 23 days in hospital. During the first week, before the inception of chemotherapy, the patient was the source of infection in 5 secondary cases. Two doctors, two nurses and one patient became ill with infections of the throat from which streptococci of Type 14 were isolated. No secondary cases occurred after the inception of chemotherapy.

This patient is an excellent example of a dangerous carrier giving rise to secondary cases and of a case in which the infection causing the spreading was localized not only to the respiratory tract but also to the skin.

Case 26. A boy aged 9 months with a history of eczema. Admitted to hospital on November 15, 1946. He had then been suffering for some time from symptoms of bronchial asthma and a watery secretion from the left nostril. There was a simultaneous flare-up of the skin lesions, particularly in the face, on which purulent vesicles appeared on the day before admission. On the same afternoon his temperature was 38.9° C.

At the first examination on admission, the clinical picture was entirely dominated by the purulent and watery eczematous lesions. No secretion from the nose was found and the throat was only moderately red and swollen. Bacteriological cultures taken on the following day nevertheless revealed abundant streptococci from the nose and throat. The child was also shown to be a dangerous carrier. Numerous streptococci were found in the dust and air of the ward. Two days after admission the child in the adjacent bed developed rhinitis and plentiful streptococci were then isolated. Owing to the spontaneous agglutination of all the strains isolated, no typing could be made in this case. The patient may, nevertheless, be considered as typical of a dangerous carrier in whom the symptoms of infection of the respiratory tract are relatively slight.

Case 17. A girl aged one year. The patient had frequently suffered from eczema since the age of 3 months, with a definite

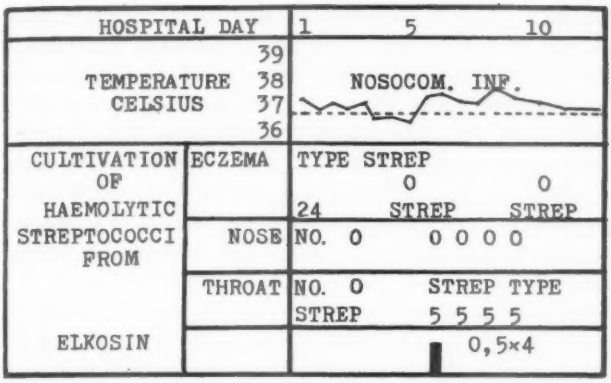

Fig. 5. Clinical data in typical case of nosocomial streptococcal infection. Elkosin = 6-sulphanilamido-2-4-dimetyl-pyramidine.

exacerbation after the intake of oranges. She was admitted to hospital on October 23, 1946, owing to an exacerbation of the eczema and a subfebrile temperature. The most important clinical data are assembled in Fig. 5.

On admission the picture was entirely dominated by the skin lesions. On the hands, the folds of the knees, and around the genitalia the skin was swollen and reddened and covered partly with purulent vesicles slightly more than a hemp-seed in size and partly with crusted areas up to 1.5 cm in diameter. The volar aspect of both hands was covered with a watery discharge. Other than a slight reddening of the throat no signs of respiratory tract infection were found. The microsedimentation rate was 28 mm/hr. On the first day in hospital the temperature was 37.8° C but was thereafter normal. Abundant streptococci of Group A, Type 24, were isolated from the discharging areas of the skin on the day of admission. Despite repeated cultures, no streptococci could be isolated from the nose or throat. On October 29 the antistreptolysin titer was 500 U/ml.

The eczema rapidly cleared up and no streptococci could be isolated after 5 days. On the fifth day there was a rise in temperature to 37.7° C and pharyngitis was diagnosed. Streptococci

of Group A, Type 5, were isolated and found regularly until the child was discharged from hospital. The fever coincident with this infection lasted for 5 days, after which no objective throat symptoms were found. The source of infection was presumably one of the doctors, who had become ill a few days earlier with rhinopharyngitis, streptococci of Type 5 being isolated. Two days after Case 17, a child in another room in the same ward as it developed streptococcal pharyngitis of Type 5. Streptococci of Type 5 were found in the air of the room the day before Case 17 became ill.

The child in this case was admitted to hospital because of an infected eczema in which streptococci of Type 24 played a rôle. During her stay she became nosocomially infected with streptococci of Type 5 found in the air of the ward in which she was nursed.

Case 21. A boy aged 13 months who was admitted to hospital on November 4, 1946, for observation on the grounds of suspected mongolism. He had not suffered from any infection shortly before admission nor were there any symptoms of throat infection at the first examination. Repeated cultures from the nose and throat were negative in respect to haemolytic streptococci. After 14 days in hospital an acute infection developed. His temperature was 38.6° C and there was a thick, purulent nasal discharge and a reddened throat. Abundant streptococci were found on the first day in cultures from the nose and throat and the child was found to be a spreader of infection. The fever lasted for 3 days, and the rhinitis, which was the predominating symptom, for 12 days. The microsedimentation rate rose during the first two days of the infection to 47 mm/hr and the W. B. C. to 15 000. Streptococci were isolated from both nose and throat during the first 6 days but thereafter only from the throat. The child was a spreader of infection as long as the cultures from the nose were positive but not later. As long as the spreading test was positive, plentiful streptococci were found in the dust and air. The probable source of infection was Case 26, described earlier.

Case 21 is a typical example of a child admitted for observation and infected nosocomially during his stay in hospital owing to

the admission of a dangerous carrier to the same ward. The patient was a spreader of infection during the acute stage of the illness.

Case 30. A newborn boy (born 9 weeks before term) admitted to the hospital on August 22, 1946, because of prematurity. The mother was employed as a wet-nurse and the infant therefore spent a very long time in hospital. It was not, however, possible to isolate haemolytic streptococci from his throat earlier than 4 months after admission. No clinical symptoms appeated but the child was throughout entirely healthy. Subsequently streptococci were isolated regularly from his throat for nearly 5 months until he was discharged from hospital. Bacteriological cultures from the nose were consistently negative and the child could not be shown to be a spreader of infection. The mother was the probable source of infection. It is of some interest to note that she was a carrier of streptococci in the throat long before her child. As long as the culture from the throat alone was positive she was only a harmless carrier. At the end of December she became ill with acute tonsillitis and streptococci were then isolated from the nasal mucosa as well. She thereupon became a spreader of infection and a few days later streptococci were found for the first time in cultures from the throat of her child.

This case is typical of a nosocomially infected harmless carrier who gave rise to no secondary cases.

Clinical Symtoms

The Patients. The majority of infections were relatively mild. Thirty of the 75 children from whom streptococci were isolated were healthy carriers. The most common clinical characteristics were the following.

Type of Infection. The overwhelming majority of cases were in the form of pharyngitis, rhinopharyngitis, or tonsillitis. In a small minority of instances the clinical picture was not dominated by infection of the throat but by some symptom in which streptococcal infection was presumably the exciting factor. Five children, for example, were admitted under the diagnosis of

bronchial asthma and two of croup. Infected eczema was the cause of admission in two cases and infected skin-lesions in two others. One child was admitted with suppurative otitis. Clinically, no difference was found between primary and nosocomial infections.

Fever. The temperature was frequently high on the first days of the illness but rarely remained raised for more than 5—6 days. In many instances it had already started to fall when the child was admitted to hospital.

Nose and Throat. Clinical examination usually revealed only a reddened and swollen throat, at times with reddened and swollen tonsils. The cervical lymph nodes were enlarged and tender in some instances and a purulent nasal discharge was present in some cases.

Laboratory Findings. There was usually a moderate rise in the microsedimentation rate and moderate leukocytosis.

Therapy. Chemotherapy or antibiotics were seldom necessary. In a small minority of cases with more pronounced symptoms, Elkosin or penicillin were administered with satisfactory results.

Complications. Complications were uncommon. Suppurative otitis developed in one nosocomially infected child. Only in two instances did the streptococcal infection give rise to more severe sequelae, i. e. polyarthritis in one case and haemorrhagic nephritis in another.

Personnel. It was not possible to follow the clinical symptoms as closely in the case of the personnel as in that of the children, since many of the former were nursed at home. Healthy carriers were common. The infections were of the same type as in the children, i. e. pharyngitis, rhinopharyngitis, and tonsillitis. The symptoms were often mild and seldom caused an absence from work of more than one week. Those of the personnel who worked at the hospital for long periods usually suffered from a streptococcal infection on at least one occassion and often on several.

Streptococci in the Dust. The results of analyses of the dust in both units are seen in Figs. 6 and 7. Four hundred and thirty specimens, of which 75 contained streptococci, were examined from Unit I. Four hundred and thirty two tests were made from

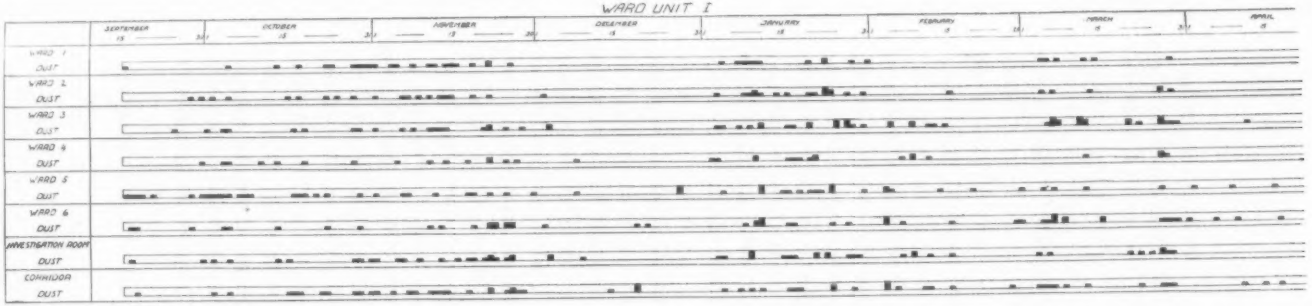

Fig. 6. Diagram showing occurrence of β-haemolytic streptococci in hospital for children. Bacterial content of dust (sparse, moderate, abundant) is evident from height of respective black columns.

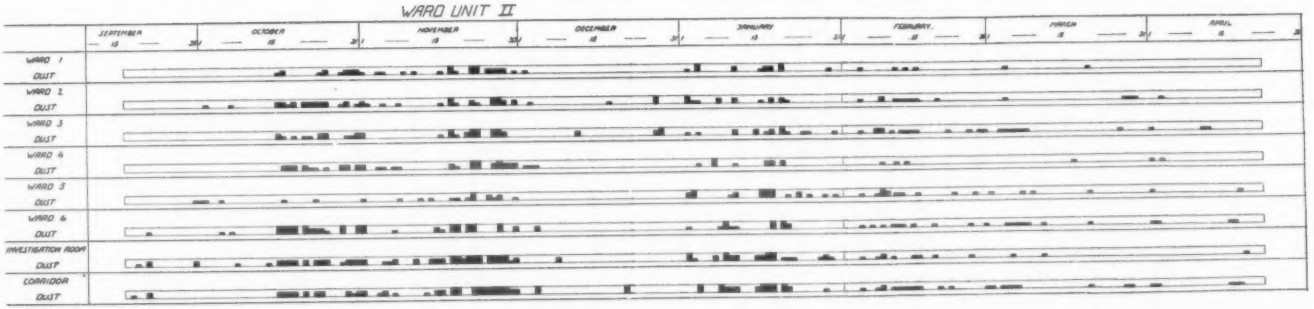

Fig. 7. Diagram showing occurrence of β-haemolytic streptococci in hospital for children. Bacterial content of dust (sparse, moderate, abundant) evident from height of respective black columns.

Unit II; 105 contained streptococci. It will be seen from the figures that streptococci were found relatively constantly during certain periods both in the oiled and in the unoiled ward units. Longer or shorter free intervals occurred. At times large quantities of streptococci were found in the dust. This occurred particularly during periods when so-called spreaders were nursed in them. For example, only 24 hours after Case 13 was admitted, streptococci were isolated from the dust not only of the ward in which he was nursed but also in the other wards in the same unit, although this unit was oiled.

Even during periods in which no spreaders of infection were nursed in the units, streptococci were found in the dust, although in smaller quantities. This was, for example, the case in Unit I in September 1946. Streptococci of Types 4 and 12 were then isolated from the dust in several wards. At the same time streptococci of Type 4 were isolated from two children and Type 12 from one child and one nurse. None of them could be shown to be spreaders.

On those occasions on which the streptococci were typed, the same types were usually found in the dust as in the patients and the personnel. With the method used, certain rough quantitative differences in the bacterial content could be demonstrated under certain conditions. An analysis of this kind roughly reflected the incidence of streptococci in the patients and the personnel.

Streptococci in the Air. Both Bourdillon's slit sampler and ordinary sedimentation plates were used to demonstrate the presence of streptococci in the air. Such controls were not made in all the wards but mainly in those in which infected patients were nursed and in the connecting corridors. In Ward Unit I, 54 experimental sereis were made with the slit sampler on different days. Streptococci were demonstrated in 10 of them. The corresponding figures for Ward Unit II were 199 experimental series of which there were 78 with streptococci. The results using sedimentation plates were the following: Ward Unit I: 460 experimental sereis, 26 positive; Ward Unit II, 470 experimental series, 125 positive.

A comparison between the results with the two methods is

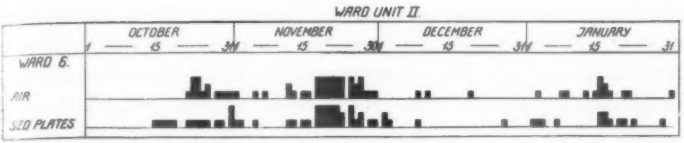

Fig. 8. Investigation of β-haemolytic streptococci in air in ward for children. Slit sampler method (air) compared with open plate method (sed. plates).

given in Fig. 8. It will be seen that the results were as satisfactory with the sedimentation plates, which are very easy to handle, as with the specially-built Bourdillon apparatus. The simple sedimentation plates proved in practice to be very suitable for continuous control of certain pathogenic bacteria in the air. When dangerous carriers were found in the ward units, this was reflected very rapidly in the sedimentation plates and a quantitative rough estimate was possible. As was the case in the analysis of the dust, this is illustrated very well by Case 13. As soon as 24 hours after his admission, numerous streptococci of Type 14 were found in the air of all the wards in the unit. During the preceding week no streptococci had been present in the air despite daily controls.

Bourdillon's slit sampler was nevertheless necessary for more detailed studies, particularly in respect to the periods of the day during which the greatest amount of streptococci could be demonstrated in the air.

Streptococci could be demonstrated more frequently in the oiled ward unit both with analyses of the air and of the dust. Despite oiling, the spreading of streptococci to all the wards through the air could not be prevented when spreaders of infection were present.

Discussion

A detailed bacteriological study with particular reference to streptococcal infections was made in two ward units of a children's hospital during the autumn of 1946 and the spring of 1947. Oiling of the floors and textiles was used as a dust control measure in one unit, while the other served as a control. The results of the tests showed that the frequency of nosocomial infections was

4.9 % for the children in the oiled unit and 2.9 % in the control unit. The corresponding figures for the personnel were 28.8 and 25 % respectively. There was thus a larger number of nosocomial infections in the oiled unit among both the children and the personnel. These results are in agreement with those of the control experiments of BEGG, SMELLIE, and WRIGHT in England and of the Commission on Acute Respiratory Diseases in the U. S. A.

Analyses of the dust and air revealed a relatively constant presence of streptococci during certain periods interrupted by long or short free intervals. Streptococci were found in particularly large quantities during periods when so-called spreaders of infections were nursed in the units. Thus, for example, 24 hours after the admission of a spreader of infection, streptococci were isolated from the air and dust and were rapidly spread over the entire ward unit. This was not prevented by oil treatment of the floors and textiles. During the periods when numerous streptococci were found in the air and dust nosocomial infections were prevalent.

It was possible to confirm the criteria for spreaders of infection set up by Hamburger and co-workers, i. e. that bacteria are usually present in the nasal mucosa and can also be isolated from the upper lip, hands, and clothes. It was also shown that infections at other sites than the respiratory tract may cause a carrier to become a spreader. For example, the child who was the most dangerous spreader in the present study and who gave rise to the largest number of nosocomial infections suffered from allergic purpura infected by streptococci. It is therefore of prime importance in every kind of infection to ascertain whether the patient will spread the infection.

Even during the periods when no spreader was nursed in the units, streptococci were found in the dust and air, although to a lesser extent. Possible explanations are that a number of the children or the personnel were only spreaders of infections on some occasions, a fact that could not be ascertained with the methods used, or that the streptococci occurring in the dust survived for an unusual length of time. For practical epidemiological purposes it may therefore be useful to divide infected persons

into the following 3 categories: 1) persistent spreading carriers — dangerous carriers, 2) transient spreaders of infection, and 3) non-spreading carriers. This classification has been set up and tested in practice by OUCHTERLONY (11) in investigations on diphtheria.

In the case of streptococci, the spreading properties are not dependent on the presence of an acute infection. They can occur both in acutely infected as well as in healthy carriers. In several cases, for example, no spreading could be demonstrated even in the most acute stage of the illness. In other cases there was considerable spreading by carriers who were free from clinical symptoms.

The present study also revealed that, as regards the spreading of streptococci, the value of the oil impregnation of blankets and bedclothes and the oiling of floors cannot be considerably as sufficiently established as yet.

In order to combat nosocomial infections of this kind more successfully, it is necessary to keep the ward units free from spreaders of infection. An investigation on admission should reveal the presence of such a spreader before he has had the opportunity of spreading bacteria in the wards. A spreader thus found should be placed in an isolation room and treated with chemotherapeutic agents or antibotics that have proved effective in such cases. When the patient no longer spreads bacteria, he can be put with other patients. Continuous checks of the air dust can provide valuable information for the detection of spreaders of infection.

Summary

An investigation into the control of dustborne haemolytic streptococci was carried out in two identical children's wards during the autumn of 1946 and the spring of 1947. In one, the oiled ward, all the bedclothes and ward linen were treated in the hospital laundry with Triton oil and the floor of the ward unit was oiled. In the unoiled ward no anti-dust measures were taken.

The investigation showed the following:

1. the number of nosocomial infections was not affected by the steps taken;

2. the presence of a dangerous carrier was of decisive importance in accounting for nosocomial infections;

3. consequently, in judging the value of prophylactic measures, no conclusion may be drawn without consideration of the decisive importance of dangerous carriers.

Résumé

Durant l'automne 1946 et le printemps 1947, on a fait dans deux sections identiques d'enfants, des recherches en vue du contrôle de la création par la poussière, des streptocoques hémolytiques. Dans l'une des sections, celle que l'on avait huilée, toute la literie et tout le linge de la section étaient traités à l'huile Triton, dans la buanderie de l'hôpital, et tout le plancher de la section était huilé. Dans la section non huilée, on n'avait pris aucune mesure anti-poussière.

Les recherches ont montré ce qui suit:

1. Le nombre des infections nosocomiales n'était pas affecté par les mesures prises.

2. La présence de porteurs dangereux était d'une importance décisive pour les infections nosocomiales.

3. Par conséquent, dans l'appréciation de la valeur des mesures prophylactiques, on ne doit pas tirer de conclusion sans considérer l'importance décisive des porteurs dangereux.

Zusammenfassung

Zur Kontrolle der im Staub enthaltenen hämolytischen Streptokokken wurde in 2 identischen Kinderabteilungen im Herbst 1946 und Frühling 1947 eine Untersuchung durchgeführt. In der einen, der "geölten" Abteilung, wurde alle Bett- und Gebrauchswäsche in dem Spitalswaschhaus mit Triton-Öl behandelt und alle Fussböden der Abteilung geölt. In der "ungeölten" Abteilung wurden keine Anti-Staub-Massnahmen getroffen.

Die Untersuchung zeigte Folgendes:

1. Dass die Zahl der nosokomialen Infektionen von den Massnahmen nicht beeinflusst wurde.

2. Dass die Anwesenheit von Bacillenträgern von entscheidender Wichtigkeit für die Erklärung nosokomialer Infektionen war.

3. Dass infolgedessen bei Beurteilung des Wertes prophylaktischer Massnahmen kein Schluss gezogen werden darf ohne den entscheidenden Einfluss der Bacillenträger zu berücksichtigen.

Resumen

En dos guarderías infantiles idénticas fué llevada a cabo, durante el otoño de 1946 y primavera de 1947, una investigación para el control de la estreptococia hemolítica ocasionada por el polvo. En una de ellas, la guardería impregnada con aceite, todas las sábanas y ropa blanca fueron tratadas en la lavandería del hospital con aceite "Tritón" y fué impregnado el piso de la guardería con aceite. En la otra, no impregnada con aceite, no fueron tomadas medidas contra el polvo.

La investigación ha demostrado lo siguiente:

1) que el número de infecciones nosocomiales no fué afectado por las medidas adoptadas;

2) que la presencia de un contaminador (portador de gérmenes) era de decisiva importancia en lo que afecta a casos presentados de infecciones nosocomiales;

3) que, consecuentemente, para juzgar el valor de las medidas profilácticas, no deben extenderse conclusiones sin antes considerar la decisiva importancia de los contaminadores.

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FROM THE CHILDREN'S CLINIC OF THE UNIVERSITY, HELSINGFORS.
(CHIEF: PROFESSOR A. YLPPÖ.)

On Tuberculosis in BCG Vaccinated Children

by

OLE WASZ-HÖCKERT

During and after the Second World War tuberculosis morbidity and mortality increased greatly in the war-swept countries. The battle against this disease, now so prevalent, should be fought by every available means. In countries with a high or normal standard of living efforts are still being made to ameliorate the situation. Mass x-ray examinations and prophylactic inoculation with BCG vaccine are the weapons which are expected to yield the best results.

In the Scandinavian countries BCG vaccination has now been used extensively according to the directions given by WALLGREN and HEIMBECK in 1927 for more than 20 years. The most valuable contributions to the Calmette literature have been supplied by Scandinavian investigators (HEIMBECK, WALLGREN, SCHEEL, TÖRNELL, NORDWALL, WINGE, HOLM, HYGE, MALMROS, BESKOW, and others). Their studies show that prophylactic inoculation with BCG vaccine gives *good relative protection* against primary tuberculosis and also against forms of post-primary tuberculosis In HYGE's investigations there is adequate comparative material, but in this respect the reports of American authors are of special interest (FERGUSON, ARONSON, and ROSENTHAL) inasmuch as they append control material identical from a statistical point of view. In all these works the results confirm the effectivity of BCG vaccination beyond any doubt.

Yet in many countries outside Scandinavia opinions diverge greatly regarding the preventive effect of the vaccination method. This is distinctly reflected in the review of the Forty-Third Annual Meeting of the American National Tuberculosis Association in

San Francisco held in June 1947. At the meeting it was resolved that the U. S. Health Service should organise long-range studies for the purpose of increasing the knowledge of the BCG vaccination method in the United States and later pass definitive resolutions on the basis of the results of these studies. The desire to test the method in native surroundings is understandable and has been followed in the majority of countries. Even in Germany BCG vaccination is now performed (KLINKE). Probably the attitude towards the method which each country finally adopts will depend entirely upon the results obtained in the different countries. On that account it would be of great value to have the results of the examinations published, particularly for the benefit of foreign research workers, so as to *bring out the sources of error*. The drawback of large investigation series and mass vaccination is that the first principles of the method cannot for practical reasons be adhered to. What has been said above shows that the material should be submitted to objective scientific analysis for the purpose of obtaining as complete a picture as possible of the preventive effect of vaccination. *Cases in which the effect of BCG vaccination has failed should be illustrated by detailed histories.* Objectivity requires, moreover, that *the cases of tuberculosis in the control groups* also be accompanied by relevant historical data, for the purpose of excluding all doubts regarding the diagnosis. This demand has been quite rightly voiced by MEYERS. It has been stated earlier (IMERSLUND, BIRKE, DIFS, TÖRNELL, and WASZ-HÖCKERT) that if BCG vaccinated children have become infected with tuberculosis, it is due to the vaccination not having been carried out lege artis, or the inoculation has been done during the prae-allergic phase. As it is impossible to avoid vaccinating an already exposed although tuberculin-negative reactor, this fact has to be taken into consideration in evaluating the results. This was not done, however, at the meeting in San Francisco. The opposers of BCG vaccination based their opinion principally on LEVIN and SACKLETT's investigation and it should be observed that the patients reported in their studies who died of tuberculosis had been *exposed to infection before or during the period of vaccination.*

A paper published by TÖRNELL in 1947 gives a complete survey of the entire Calmette literature. He is the first author to mention the size of the local vaccination scar and the strength of the tuberculin sensitivity in control tests. This allows evaluation of the strength and durability of the immunity. Works by HOLM, ARONSON, and ROSENTHAL, among others, have been published since. Adequate control material is lacking in the majority of the papers, but on the whole it may be noted that *in the non-vaccinated cases there have been about 8 times as many cases of tuberculosis and deaths from tuberculosis as among those vaccinated.* It should be noted that no Scandinavian author has as yet mentioned death of tuberculosis in a BCG vaccinated patient. The figures naturally vary among the authors, due to differences in the age, exposure, and race of the patients. Moreover, the virulence of the vaccine varies in different countries and laboratories, and different techniques are used by different vaccinators both as regards dosage and the intracutaneous injection technique itself. Lastly, the results are dependent on varying tuberculin tests.

In view of the above, the statement may be repeated that BCG vaccination gives good *relative*, although not complete, protection.

BCG vaccination was adopted in Finland some years ago as a weapon in the prophylactic battle against tuberculosis. Deaths from tuberculosis, which up to 1939 were about 15/10000 inhabitants, increased during the war by — according to calculation (WASZ-HÖCKERT) — 11-12 per cent. Housing difficulties, which do not seem to improve, increase the danger of infection, and the sanatoriums have too few beds. All these factors contributed to the decision to inaugurate vaccination on a large scale, a decision strengthened by the fact that a Finnish investigator found that BCG vaccination gave recruits good protection (SAVILAHTI). Under the conditions now prevalent the vaccination cannot, however, always be carried out in such a way as to guarantee the best possible qualitative results. And since failure, even if only in solitary cases, might discredit the method, it seemed advisable to the present author to study whether tuberculosis occurred in patients vaccinated with BCG at the Children's Clinic and, in this connection, to discuss error in vaccination and diagnosis.

Material

During the period January 1944 to May 1948 about 11 600 patients were treated at the Children's Clinic of the University of Helsingfors. About 500 of these children suffered from tuberculosis in some form, and about 60 per cent of these from primary tuberculosis. In this investigation I have studied 23 *cases* of BCG vaccinated children who were admitted to the hospital because tuberculous disease was suspected or because their symptoms during their stay in the hospital pointed to tuberculous etiology. Their past histories were checked in maternity hospitals and child-care advice centres and the parents and dispensary physicians were questioned. Some patients were called for check-up examination. The hospital's roentgenologist, Dr Heikel, has very kindly assisted me in evaluating the results of these and earlier x-ray materials. Dr Ahvenainen, pathologist to the clinic, subjected the post mortem material still available to renewed histopathological examination.

I. Death From Tuberculosis Despite BCG Vaccination

Results

Not one single death of a BCG vaccinated patient has been reported from Scandinavia. Such cases have, however, occurred in America. Unfortunately detailed hospital records are as a rule lacking, and in consequence criticism of these cases is rendered impossible. The present investigation from Professor Ylppö's clinic includes one case of a child vaccinated with BCG who died of tuberculous meningitis.

Case 1. Boy, born August 1, 1947. Tb diagnosed in father, now under treatment in sanatorium, in May 1948. Twin-birth. Weight at birth 3400 g, development normal. BCG vaccination by paediatrician August 4, 1947. Mantoux 0.1 mg positive on October 9. A small, slightly reddened local infiltration noted at site of injection. — On February 20 temperature; treated with sulfonamide until fever disappeared on February 23. On February 25 somnolent, glassy eyed. Admitted to Children's Clinic on following day. Weak, fontanelle pressure increased, neck

stiff. In liquor Nonne and Pandy positive, lumbar sugar 0.027, WBC count 109 (84 per cent lymphocytes). X-ray of lungs showed blocking of hilus. Meningeal symptoms increased and death followed on February 29. *Post mortem examination* revealed necrotic glands in region of bifurcation and symptoms of tuberculous meningitis. Diagnosis confirmed by Dr Ahvenainen's histo-pathological examination. — The twins had shared a bed and used the same teat but the second child, also vaccinated with BCG August 4, 1947, remained healthy. This child — a girl — was examined May 1948 and found to be quite well, also roentgenologically, but strong reaction to Pirquet and Mantoux 0.1 mg points to superinfection.

Summary: A lege artis BCG-inoculated boy of 6 months died in the hospital of tuberculous meningitis 6 months after having been vaccinated. The diagnosis was confirmed by post mortem examination and histopathological examination. His twin sister was BCG vaccinated at the same time but did not become ill with tb even though she was distinctly superinfected.

II. Tuberculosis Despite BCG Vaccination

The following are the case histories of BCG vaccinated children at the Children's Clinic for Tuberculous Diseases.

Case 2. Girl, born September 1941. Maternal grandfather and uncle died of tb. Parents former pneumothorax patients. Mother, sputa positive —35. Patient's younger sisters and brothers healthy, BCG vaccinated. Girl was vaccinated at age of 5 weeks; Hamburger's test negative. About 2 months later Mantoux 0.1 mg positive. Admitted January 23, 1945 to Maria Hospital following fever of 4 days' duration. 1 week before admission patient roentgenologically negative upon examination by specialist at dispensary. In Children's Department subfebrile, S.R. 40/—, Hamburger's test and Pirquet negative, but Mantoux 0.1 mg positive. X-ray of lungs January 24, 1945: distinctly enlarged, demarcated hilar glands bilaterally. Discharged after pertussis incubation. In August of that year general condition good, S.R. 5/—. Later quite well on whole. Admitted to Children's Clinic February 22, 1947 on account of pneumonia. Pirquet negative, Mantoux 0.1 mg negative, but Trambusti positive on March 8. High fever rapidly reduced with sulfathiazole. X-ray examination showed diffuse bronchopneumonia in lower part of lung on right. X-ray check-up on March 15 showed that the focus had disappeared but the status of January 1945 remained. Treated after

discharge March 20 in sanatorium for children. General condition good all the time. Summoned for follow-up on March 17, 1948, i. e. about 3 years after first becoming ill. General condition good, no BCG vaccination scar. X-ray check-up: hilar contours unchanged for 3 years, signs of beginning calcification.

Summary: A child of 3 $^1/_2$ years. Pneumothorax treatment of parents already terminated. BCG vaccinated at age of 5 weeks, afterwards tuberculin positive. Nothing noteworthy observed in x-ray of lungs 1 week before initial fever stage. Primary tuberculosis with benign course. Followed roentgenologically in connection with pneumonia 2 years later. At check-up 3 years after inception of disease x-ray diagnosis still verifiable. — Younger sisters and brothers BCG vaccinated, all quite well, nothing pathological observed in x-ray examination.

Case 3. Boy, born January 24, 1944. Maternal grandmother died of tuberculosis before child's birth. No known exposure to tb. Younger sister healthy. Patient BCG vaccinated shortly after birth. No subsequent tuberculin test. Admitted to Maria Hospital on account of eczema May 1945. Two fluoroscopies of lungs showed nothing exceptional. Hamburger's test and Pirquet negative. Mantoux 0.1 mg positive. Inoculation scar not examined. In October 1946 patient had transitory fever and erythema with itching red nodules on anterior side of lower legs. Following 3 days of fever at home admitted to Children's Clinic November 5 with high temperature and erythema nodosum nodules on anterior side of lower legs and thighs. Percussion sound shortened over lower part of left lung. No symptoms of meningitis. S. R. 71/—, Pirquet positive, and according to roentgen picture pleuritis on left. Test puncture: serous liquid, bact.: —. Widal and Weil-Felix negative, cold agglutination reaction normal. Lumbar puncture: nothing noteworthy. Free of fever in about 3 weeks, S. R. high over long period. On X-mas day no free liquid. Repeated x-ray examination at short intervals. On discharge, January 4, 1947, very slight remains of pleuritis laterally but hilar adenitis on left stationary. When discharged general condition good.

Summary: The patient, a boy of 3, was BCG vaccinated shortly after birth. At the age of somewhat over a year Mantoux 0.1 mg positive, lungs roentgenologically free. After initial fever with mild course and erythema nodosum-like eruptions, admitted 2 months later with left-sided exudative pleuritis and several erythema nodosum eruptions. Fever for a period of 3 weeks. Clinical

and roentgenological regression of the exudate in about 2 months but persistent hilar adenitis. — As patient's general condition was good and as nothing suggesting pneumonia-pleuritis was present, the tuberculous etiology of pleuritis despite BCG inoculation was established.

Case 4. Boy, born April 17, 1947. Mother x-rayed during pregnancy. No pathological findings. Infant BCG vaccinated shortly after birth. After delivery the mother was removed to the Children's Clinic where she acted as wet-nurse, the baby being nursed in the department for uninfected infants. Normal development. At age of 5 months Pirquet positive, 2 febrile periods. 1 month later tuberculous process discovered in mother's lungs. She was at once removed to a sanatorium. First x-ray of infant October 10, 1947: left hilus slightly enlarged, also hypertrophy in paratracheal region on right. Fortnight later changes somewhat more marked. Removed early in December to Children's Department of Helsingfors Hospital for Tuberculous Diseases. X-ray changes remained stationary. Child's general condition throughout good, no fever, but S. R. high, having been normal before discovery. — In May 1948 no vaccination scar, x-ray picture unchanged.

Summary: Primary tuberculosis with benign course in child of tuberculous wet-nurse. Mother became ill with tuberculosis probably about 6 months after delivery. She had not infected anyone in the ward where she was assisting with the cleaning. — The case is of interest as the disease was discovered on account of the mother's tb. There were no clinical signs of tb (no initial fever) other than x-ray findings and a high S. R. Gastric washing examined in native preparation and cultivation but no positive findings. Stationary x-ray findings confirmed the diagnosis, however. — Roentgenologically ascertained primary tuberculosis without a marked period of fever and with an increased sedimentation rate at the time of the allergic change, is rather exceptional at this age (GYLLENSWÄRD Jr.). In this case the course is somewhat obscured by the BCG vaccination.

Case 5. Girl, born March 8, 1943. Mother treated for pneumothorax. Patient vaccinated in spring 1945. Pre-test: 1,0 mg Mantoux, afterwards tuberculin positive, distinct scar (3 × 3 mm) after suppuration. Whooping cough following year. Fever April 1947. Admitted to Children's Clinic October 14 after some period of lassitude. General condition good, how-

ever. Pirquet positive, slightly subfebrile, S. R. 14/—. X-ray examination showed marked swelling of the hilus on right and distinct interlobular shadows. — Discharged for convalescence at home 1 week after admission. X-ray check-up in May 1948: status quo.

Summary: Girl, aged 4, evidently exposed to tuberculosis by her mother. Her initial fever period probably occurred in April 1947 before admission to Children's Clinic 5 months later; somewhat tired (and slightly febrile ?). The interval between the initial fever and pleuritis fits in well. Signs of previously resorbed, limited interlobular pleuritis observed in hospital. Clinical course and x-ray check-up May 1948 confirmed diagnosis.

Case 6. Boy, born June 5, 1943. Paternal grandfather and aunt died of tb about 30 years before. Exposed to tb by boarder. BCG vaccinated by dispensary physician Autumn 1946, Pirquet negative. No check-up test. In April 1947 fever which disappeared following sulfathiazole medication. In beginning of June new period of fever not influenced by sulfathiazole. Admitted to Children's Clinic on June 7, 1947: subfebrile, general condition fairly good. Pirquet positive: S. R. 67/—. Treated for 1 month in hospital: fever receded gradually, S. R. remained high. Cold agglutination reaction normal, eosinophilic cells 1 per cent. Gastric washings examined on July 12 and 24: native preparation and cultivation negative. Child admitted for follow-up examination 6—9 September. General condition good. Pirquet positive. S. R. 32/—. X-ray examined 4 times between July 9 and October 7. On left, in lower part of lung, extensive parenchymal infiltration with swelling of hilus on same side. Roentgenological findings almost unchanged during whole time. New check-up in July: status quo.

Summary: BCG vaccinated boy, aged 4, became ill 8 to 9 months after vaccination with a disease of the lungs of primary tuberculosis type. Stationary roentgen course strongly indicative of tuberculous etiology.

Case 7. Boy, born September 3, 1946. No known exposure to tuberculosis. Parents and sister aged 5 months well. BCG vaccinated at age of 3 months, no check-up. Earlier well but became ill on February 27, 1948 with fever. Upon admission on following day 39.6° C. Sulfathiazole treatment of little avail. By means of fluoroscopy district specialist in tuberculous diseases found swelling of hilus and signs of parenchymal changes. Child admitted to Children's Clinic on March 6. General condition poor, pronounced nose-wing-breathing and in left lower part of

lung percussion sound shortened and dry râles. No meningeal symptoms, Pirquet positive, S. R. 45/—, highly febrile. Pleural puncture: cloudy exudate (Rivalta positive), no bacterial findings. Liquor findings negative. Died March 22. X-ray examined March 8 and 15. On right parenchymal blocking in progressive stage; in later examination small infiltration in caudal direction on left side. Both hili enlarged. Macroscopically cheese-like focus size of pea was found. Microscopic examination by hospital pathologist, Dr Ahvenainen, showed that necrosis was of tuberculous nature but according to him tuberculous changes in pneumonic sections were not statable histologically.

Summary: Boy of 18 months was vaccinated but not given a check-up tuberculin test. Admitted to hospital following short period of fever in poor condition and with distinct symptoms of pneumonia. Died within a fortnight, the disease picture showing pneumonia. Upon post mortem tuberculous necrosis the size of a pea was found in addition to pneumonic changes. In this case the histopathological examination established the fact that the cause of death was pneumonia and the tuberculous focus a secondary finding.

Discussion

In discussion of BCG vaccination the commonest argument against the procedure is that it renders the diagnosis of tuberculosis more difficult or impossible. The tuberculin test is the most reliable diagnostic aid we have in tuberculous infection in children and a most valuable weapon in mass examination. We know that the protective effect of BCG vaccination is so good that tuberculosis seldom occurs in correctly BCG vaccinated persons. For that reason the diagnosis tuberculosis in such subjects should be regarded as somewhat doubtful. If the fever remains constant and the x-ray findings are suspicious, the case should be studied in a hospital for children.

When uncertain cases of this description are sent in for clinical investigation the diagnosis will be greatly facilitated by the following information.

1. BCG inoculation.

What tuberculin tests were made before vaccination?

When, how, and with what results was the check-up test performed?

To what extent was the patient exposed to tb before the vaccination »took»?

2. Did the first symptoms of disease appear within or after a period of 3 months counted from the time of vaccination?
3. Was there any local reaction or local scars?
4. What was the patient's sensitivity to tuberculin?
5. Has any tendency towards roentgenological regression been noted?
6. Was the fever sensitive to chemotherapy or to penicillin?

The vaccination must be carried out according to certain given principles before a patient suspected of tuberculous disease can be considered BCG vaccinated. The first condition is *negativity to tuberculin before the vaccination.* A negative reaction to percutaneous tests excludes tuberculous disease only during a fairly active phase — for instance, primary tuberculosis in the initial febrile stage and during the following months. Primary tuberculosis in the process of healing usually fails to give a positive result when ointment and patch-tests are used. A negative Pirquet test or Mantoux 0.1 mg excludes almost with certainty a healed infection; complete certainty is probably obtained by 1.0 mg Mantoux. The second condition is that the vaccinated child has *become positive to some tuberculin test after vaccination*, preferably within a period of $1\,^1/_2$ to 3 months. If there is good local reaction the tuberculin test is not absolutely necessary.

If possible to obtain information as to whether or not the vaccinated child has been exposed to virulent infection is of importance. It is well known that the incubation time of tuberculous infections covers a period of 5 to 6 weeks and that tuberculin positivity does not set in until at the earliest 6 weeks after the inoculation. Hence it is evident that when *a tuberculous disease* (the first symptom of which is the initial fever) *sets in 3 months or less after the vaccination, this cannot be due to failure in BCG protection.* The case is quite the reverse; the patient was infected *before* the protective effect had set in. This is generally known

but deserves mentioning in this connection. It is likewise important to study the *local reaction after the inoculation.* A violent reaction at the site of the BCG vaccination — Koch's phenomenon — is a sign that a person infected with tuberculosis has been BCG inoculated. It is more common, however, for the local reaction — which in normal cases takes place 5 to 6 weeks after inoculation — not to appear until 1 or 2 weeks later when vaccination takes place in the prae-allergic phase. In addition to local reaction sensitivity to tuberculin sets in exceptionally early after inoculation which should be noted.

TÖRNELL points out that a distinct local reaction, a scar, and a strong reaction to tuberculin after the vaccination (a result of the patient's immune biological state and the vaccine dose?) are signs of better, and more lasting protection. If a febrile tuberculin-positive child with suspicious x-ray findings in the lungs has a large scar following BCG vaccination the diagnosis tuberculosis should, in the first place, be regarded as somewhat doubtful. If on the other hand, no distinct scar is visible, there may be reason for suspicion, particularly if the tuberculin sensitivity was very low after the inoculation, for instance 1.0 mg Mantoux. The tendency in Denmark is to revaccinate if a person vaccinated some years previously is not positive until 1,0 mg Mantoux is given (HOLM). It may also be mentioned that if a tuberculous affection is discovered in a patient vaccinated with BCG a long time ago, say 5 to 6 years, *there is a possibility* that the BCG immunity may have expired, permitting a virulent infection to cause the disease.

The tuberculin test is without doubt of great value in uncertain cases. Intense sensitivity to ointment and 0.01 mg. Mantoux tests suggests superinfection or tuberculous affection; *week sensitivity* to 0.1 and 1.0 mg. Mantoux does not suggest tuberculosis except in the case of infants of less than 3 to 6 months, who still have weak formation of antibodies. A central broncho-pneumonia with subacute course in a child vaccinated with BCG some years earlier may be given as an example. The x-ray findings resemble those of tuberculous lymphadenitis and the general condition is not as poor as in pronounced, sudden pneumonia. But the patient

does not become positive until 1.0 mg Mantoux is given. In such a case the diagnosis tuberculosis should not be made at once. It should be borne in mind, however, that certain states of disease weaken the tuberculin allergy.

A clinical diagnosis of primary tuberculosis based upon *one roentgen status* only is *not* reliable. The classical findings (primary focus in the parenchyma, lymphangitis, and lymphadenitis) are not very often revealed in x-ray examinations. A limited swelling of the hilus allows an x-ray diagnosis, but not, according to the majority of the authors (WALLGREN, among others), a clinical diagnosis. *One x-ray examination* (fluoroscopy and film in two directions) *of a patient vaccinated with BCG with no support from tuberculin tests* (with the reservations made above) *will not suffice to allow the diagnosis tuberculosis to be made.* A tuberculous hilus adenitis (hyperplasia lgll. bronch. tbc) will remain roentgenologically almost stationary for several years from the time of the initial fever. Calcification also will not set in until later. On that account *repeated x-ray check-ups over a long period* are of the greatest value in finding the correct diagnosis. A non-specific process in the lungs which in the beginning simulates tuberculosis roentgenologically generally decreases or disappears during treatment or at the latest in 1 or 2 months, as observed in the x-ray follow-up. A diffuse, irregular hilus blocking, shaped like the top of a mushroom, seems clinically to speak against a tuberculous etiology. In the U. S. A. there are diseases the roentgenological differential diagnosis of which is said to be extremely difficult regarding tuberculosis, particularly as calcifications appear. These diseases, histoplasmosis and coccidioidosis also give tuberculin reactions. They are very often described in the literature and should be remembered by European readers when American investigators are cited. Histoplasmin and coccidioidin reaction and rapid roentgenological regression distinguish the diagnosis.

The tuberculous initial fever, the invasion fever, is not influenced by chemotherapeutics belonging to the sulfa-group nor by penicillin. If we are confronted with a tuberculin-positive patient who runs a temperature after vaccination but obediently

reacts to the aforementioned drugs, a tuberculous etiology is not necessarily present.

From a strictly scientific point of view one should require a positive bacteriological finding before making the diagnosis tuberculosis. Even at the onset of primary tuberculosis there are positive findings in the stomach washings and even in the urine in native preparation (e. g. Nachtblau staining after cultivation ad modum Silverstolpe) and often also in the Löwenstein and guinea pig tests (RUDBÄCK). Hence in BCG examination an endeavour should be made to confirm the diagnosis tuberculosis in this manner in control material as well as in the vaccinated persons. Unfortunately it was not always possible to do so in the present investigation, owing to the fact that after the war the laboratories were not in satisfactory condition. The omission was, however, compensated for by thorough examination in every respect.

In the present follow-up examination, comprising *23 patients* treated at the Children's Clinic in whom a tuberculous disease was suspected despite BCG vaccination, 1 case was found of a child who died 6 months later of tuberculous meningitis. Furthermore, primary tuberculosis or pleuritis was discovered in 6 cases. The character of the disease was benign in all cases. The patient described last — Case No. 7 — died of pneumonia, and the post mortem examination revealed a primary focus, a secondary finding. In 2 cases tuberculin tests were not made after the vaccination, a circumstance which of course gives rise to some doubt regarding the patients' immunity. Even if these cases are included in this group, the results, in 7 cases of tuberculous disease in BCG vaccinated children, are quite good. In view of the fact that BCG vaccination is carried out on a large scale in Finland and that the turnover is very large in the Children's Clinic, including tubercular cases.

A follow-up examination of a similar kind was carried out in this country by NEVANLINNA. He collected suspected cases from different hospitals and dispensaries and found (personal communication to the author) that out of 41 cases the vaccination in about 40 per cent was so deficient that a result could not possibly be expected.

III. Cases Which Proved Non-Tuberculous Despite Suspicion

In addition to the cases described some other children vaccinated with BCG were treated at the Children's Clinic of the University of Helsingfors. These children were admitted because tuberculosis was suspected, or because some indications of tuberculosis appeared during their stays in the hospital. On the basis of renewed examinations or other circumstances the author later exempted these patients from the diagnosis tuberculosis, however.

Case 8. Girl, born February 2, 1941. Mother treated in sanatorium 7 months; never any positive bacilli findings. Later declared completely restored. No exposure known. 2 months after inoculation Pirquet test gave positive results. Suppuration of long duration in vaccination scar. Admitted to Children's Clinic with symptoms of acute bronchitis, treated July 12—20, 1945. Subfebrile on admission; S. R. 53/—; Pirquet negative; Mantoux 0.2 mg positive. Widal —. Fever disappeared rapidly, patient discharged in good general condition. Diffusely increased hilar shadows noted upon x-ray examination. In picture taken before discharge shadows greatly reduced. In check-up x-ray examination April 7, 1948 slightly increased shadow in left hilus observed but configuration not that of 3 years before. No calcifications. — Distinct vaccination scar.

Summary: A BCG vaccinated child was admitted to the hospital after having suffered from bronchitis. She was $4\,^1/_2$ years of age and her sensitivity to tuberculin was relatively low. Rapid roentgenological regression, check-up 3 years later.

Case 9. Girl, born January 16, 1944. No tuberculosis in family; no known exposure to tb. BCG inoculated at age of 18 months. Pirquet then negative, 7 weeks later Pirquet positive. In autumn 1945 frequently infections of upper respiratory tracts. Admitted to Children's Clinic on March 4, 1946, following a few feverish days. Subfebrile, S. R. 8/—, clinical symptoms of bronchitis. Negative findings in stomach washings. Discharged March 9. X-ray of thorax March 6, 1946: weak, diffusely increased hilar design resembling top of mushroom.

Summary: The suspicion of tuberculosis was abondoned when the mother stated that the child had been BCG vaccinated. Rapid roentgenological regression excludes possibility of tuberculosis.

Case 10. Girl, born April 15, 1946. No tuberculosis in environment as far as known. BCG inoculated shortly after birth. No subsequent tuberculin test but as late as April 1948 scar size of pinhead visible on thigh. Became ill March 14, 1947 with fever which disappeared with sulfathiazole medication. Relapse March 23. Admitted following day with high temperature; rapid breathing; superficial, slight nose-wing-breathing. On right over upper part of lung percussion sound somewhat shortened. S. R. 64/—; Pirquet negative; Mantoux 0.1 mg positive; WBC count 11 200. X-ray of thorax March 26: pneumonia of upper lobe or primary tuberculosis (atelectasis and hilar adenitis). Roentgenological diagnosis not possible as blocking also overshadowed hilus. Check-up April 1, 1948: parenchyma and hilus bilaterally free.

Summary: clinically pneumonia. The diagnosis was supported by the circumstances that the temperature and lung affection reacted so rapidly to pneumazol (= sulfathiazole) when the tuberculin allergy was comparatively low, and that the lungs were quite clear 1 year later upon x-ray examination.

Case 11. Boy, born November 6, 1943. Paternal uncle died of tuberculosis but was never in contact with child. No known exposure. — BCG vaccinated after negative Hamburger test. No check-up, no local reaction observed, no scar March 1948. In September fever ad 40° C reduced with sulfathiazole. Later occasional rise in temperature. Patient taken to out-patient department of the Children's Clinic October 4, 1947, treated for 10 days. General condition fairly good; temperature 37.8° C; S. R. 34/—; Pirquet —; but Mantoux 0.1 mg positive. Rapidly became free of fever following sulfathiazole medication. X-ray of thorax November 17, 1947: left lung quite free; diffuse blocking in right lung. Fluoroscopy in December of same year showed nothing exceptional in lungs. S. R. 17/—. Check-up March 18, 1948: parenchyma and hilus on right side quite free; on left side no parenchymal changes but swelling of hilus seen in both projections.

Summary: on account of the rapid clinical and roentgenological regression an inspecific infection of bronchial type — mild central pneumonia — was presumably the foundation of the disease. The changes appeared 6 months later on the opposite side. That the child actually had been vaccinated despite deficient tuberculin tests after vaccination was confirmed by the fairly weak tuberculin allergy.

Case 12. Girl, born August 7, 1945. No tb in family. Person with tuberculosis lived in same house spring-autumn 1946. Exposure possible. — In beginning of February ad 38.5° C, later occasional rise in temperature or fever ad 38° C. Tired, thinner, poor appetite. Admitted to Children's Clinic April 21, 1947. Thin, pale, Hgb 61/71, poor muscular tone. Subfebrile, S. R. 28/—. Pirquet negative, Mantoux 0.1 mg slightly positive. Mantoux 1.0 mg +. Nothing observed on percussion of lungs. X-ray of thorax April 21: »on the right anteromedially pleural rinds along the anterior wall. No pathological changes in right parenchyma. In the left lung laterally, lower part, a sharp-edged pathway springing laterally from the hilus.» Check-up May 13: »pleuritis shadow gone, hili diffusely enlarged, but no hyperplasia of gland. Parenchyma clear on left as well as on right» (Heikel). Patient discharged June 22. General condition good.

Summary: the information given in the past history constitutes a strong indication of tuberculous affection, yet tuberculous pleuritis seldom develops so rapidly in conjunction with the initial fever that an almost complete regression can be noted 2—3 months later. Complete information regarding the BCG vaccination was not obtainable in spite of extensive inquiries. It seems quite probable that the girl had pneumonic processes in February which were not adequately treated and gave rise to (mild) pneumonia-pleuritis. Her very poor general condition and the roentgenological changes also favour this assumption, particularly as rapid clinical and roentgenological improvement were noted. The roentgenologist considered a tuberculous process in the lungs excluded. — The persistent tuberculin allergy (1.0 mg Mantoux) speaks against a fresh tuberculous process but lends support to the information regarding BCG vaccination.

Case 13. Girl, born September 6, 1943. Maternal aunt died of tuberculosis 1946. Child was BCG inoculated in maternity home. Came down with measles at end of January or beginning of February. Cough and cold in head, February 20 fever for a few days. Admitted to Children's Clinic with high temperature, poor condition. Breathing superficial, rapid. Over right lung lower posterior part of lung percussion sound shortened. Pneumonic râles. S. R. 64/—; WBC count 13 700. Free of fever within two days due to pneumazol (= sulfathiazole, Orion, Helsingfors) medication; no fresh rise in temperature. — Cold agglutination reaction normal. X-ray of thorax February 25: blocking of right

lower part of parenchyma reaching as far as hilus, yet no irritation or hyperplasia of hilus. Lobular type pneumonia. Pirquet positive on admission.

Summary: pneumonia in BCG vaccinated child who may have been exposed to superinfection. Hence fairly high allergy despite measles 3 weeks earlier.

Case 14. Boy, born June 21, 1945. No tb in family. No known exposure to tb. BCG vaccinated shortly after birth. Upon check-up positive to Pirquet and distinctly fluctuating local reaction. In May small local scar. — X-mas 1947 pneumonia, which promptly receded upon sulfathiazole medication. Fresh attack of fever and symptoms of pneumonia February 1948. Treated in Children's Clinic February 3—17 with penicillin; rapid clinical improvement. Pirquet and Mantoux 0.1 negative; Mantoux 1,0 mg positive. — X-ray of thorax February 5, 1948: in field of right lung well distributed parenchymal shadows, both hili diffusely blocked. Roentgenologist's diagnosis: broncho-pneumonia, with careful reservation regarding tuberculous etiology. — In second picture on February 14 parenchymal changes had disappeared, however; still weak reaction in right hilus. Later check-ups March 9 and May 5: healed.

Summary: sulfathiazole resistant but penicillin sensitive pneumonia in BCG vaccinated boy of 3. Low sensitivity to tuberculin; distinct scar in place for vaccination.

Case 15. Girl, born August 8, 1944. No tb in environment as far as known. BCG vaccinated in maternity hospital. — Admitted December 31, 1946 to Children's Clinic following high temperature for 4 days. General condition poor on admission; rapid superficial nose-wing-breathing. Temperature 40° C. Pirquet negative, Mantoux 0.1 positive, S. R. 51/—. Free of fever in a few days due to sulfathiazole medication, rapid clinical improvement, discharged 7 days later, general condition good. — X-ray of thorax January 2, 1946: hili free, parenchymal blocking over lobe of left lung.

Summary: croupous pneumonia in BCG vaccinated child sensitive to sulfathiazole and not positive until given 0.1 mg given.

Case 16. Boy, born October 16, 1945. Eldest brother in sanatorium suffering from tb. Patient youngest of 7 children. BCG vaccinated according to information which cannot be checked. — X-mas 1946 measles, later pneumonia. In spring occasionally subfebrile, as he was before

admission May 25, 1947: tired, pale, slightly subfebrile. S. R. 25/—. Pirquet negative, Mantoux 0.1 mg positive (read off after twenty-four hours). Condition at first x-ray examination May 30, 1947 suggests primary tb: on left side somewhat more diffuse yet distinct adenitis of hilus. On right great, sharply limited swelling of hilus. Repeated tb-bac. staining and cultivation of stomach washings, results negative. Discharged July 19, preceded by check-up x-ray showing that changes on left side had disappeared completely. On right side hilus borders and those in previous picture still analogous; blocking was, however, reduced by two-thirds.

Summary: inspecific pneumonic focus in BCG vaccinated boy. Treatment brought about rapid disappearance of x-ray changes. — In other respects both past history and first x-ray pictures supported tuberculous disease.

Case 17. Boy, born August 6, 1945. Father under observation in sanatorium summer 1946 because of nodule in lung. Constantly negative bacillar findings. During stay in sanatorium the boy was BCG vaccinated. On April 1, 1947 fever resistant to sulfathiazole (pneumazol). Given penicillin in country hospital, soon free of fever. Relapse. Admitted 14 days later to Children's Clinic. April 22: tired, pale (hgb 55/65), S. R. 55/—. Pirquet —. Mantoux 0.1 positive. On percussion and by fluoroscopy pleuritis on left. Pleural puncture: pneumococci. Discharged May 12 following penicillin treatment. General condition good, no fever for about a fortnight; S. R. 35/—, percussion 0.

Summary: empyema following pneumonia. Sensitive to penicillin; pneumococci. Sensitivity to tuberculin not high enough. X-ray: hili free.

In 3 (Nos. 1563/47, 1869/47, and 60/48) out of the mentioned 23 cases information was found of the children being BCG vaccinated. They were all undoubtedly tuberculous. In the first case it appeared that the patients' elder brother had been vaccinated, but not the patient. In the other 2 cases the mothers believed, due to misleading information, that the children had been BCG vaccinated abroad. For the purpose of confirming the information inquiries were made in Sweden and Denmark and at the Committee for Removed Children in Finland. No BCG vaccination had, however, been carried out in the case of the children mentioned.

IV. BCG Vaccination of Children with Tuberculous Infection

In the material examined there were only 3 cases of children massively exposed to tuberculosis and later vaccinated with BCG, 2 of these later died of tuberculosis. The small number of deaths was due to the fact that active tuberculosis in pregnant mothers is generally discovered at the motherhood consulting centre or at the dispensaries. The newborn infants are then isolated before exposure to infection is possible. In the milieu studies undertaken by the dispensaries the children living in tuberculosis-threatened environments are subjected to examination and follow-up examination, and vaccination of such children is adequately performed. The children vaccinated as a matter of routine after negative patch tests and not isolated come from environments comparatively free from tuberculosis. *On that account* it has been possible to avoid vaccination of already infected children, or at any rate possible exposure has not lead to disease. The cases mentioned above are illustrative of this; a short case record may be of interest.

Case 18. Boy, born July 18, 1947. BCG vaccinated in maternity hospital at age of 4 days. In contact with mother who was germ-carrier (discovered later). At home seemingly well to begin with, later tired and febrile. Admitted to Clinic 30 days of age. Died on following day. Post mortem findings: abundance of miliary tubercle in lungs, liver, spleen, and kidneys.

Summary: The time of onset of the initial fever was not determinable on the basis of the past history but the disease evidently developed very rapidly. The mother had not observed any signs until a week before admission. The incubation time being, as is well known on an average 34 to 40 days (WALLGREN, WASZ-HÖCKERT), the child must have been exposed shortly after birth, i. e. before vaccination. Determination of the type of bacilli was not undertaken, but human infection must be considered indisputable on the basis of the post mortem findings. An intrauterine infection is conceivable.

Case 19. Girl, born December 12, 1944. Paternal grandfather died of consumption. Changes of tuberculous character observed in father immediately before X-mas. As bacilli findings in sputa were negative, he stayed home and was in contact with children. Patient well earlier, tuberculin negative. In middle of January 1947 she became listless, began to cough, and a few days later had a fever of 39° C. High temperature for a week which later disappeared due to sulfathiazole medication. Hamburger's test performed January 29; interpreted 2 days later as negative. On same day, January 31, patient vaccinated with BCG. On following day temperature high, 39.9° C, and she was tired and irritable. On February 2 mother discovered an abundance of papules, and skin where ointment test had been applied was vividly red. Admitted to hospital on February 3 with high temperature. Pirquet strongly positive; S. R. 40/48. Temperature while in hospital remittent; tubercle bacilli cultivated from stomach washings; bilateral hyperplasia of hilus observed roentgenologically. 10 days later x-ray examination showed well distributed miliary design in lungs. Girl transferred to hospital for tuberculous diseases; general condition very poor. — After admission primary tuberculosis discovered in her 2 sisters who were not vaccinated with BCG.

Case 20. Girl, born March 8, 1947. After death of patient infectious tuberculosis of lungs discovered in maternal uncle with whom child had been in contact. — Earlier quite well, normal development, not tuberculin tested. Became ill beginning of August with fever which despite prolonged sulfathiazole medication (40 0.5 g tab.) persisted c. 2 weeks. Later no rise in temperature observed but patient did not gain weight. Fluoroscopy by roentgenologist on August 11 in provincial town showed adenitis paratracheally on right, double-sided hilar adenitis, and »remains of pneumonia» in right lower part of lung. Tuberculosis tentatively suggested by roentgenologist. Tuberculin test had probably not been made.

Patient admitted September 9 to Children's Clinic: subfebrile; condition poor; small findings in right lung on percussion. Pirquet given same day: results negative when read off after 3 days. On September 15 Mantoux 0.1 mg also negative and at request of parents child was BCG vaccinated (0.1 cc. intracutaneously). Her general condition satisfactory at the time. Treated with penicillin, S. R. 22/—. But as early as following day vividly red infiltration arose at site of vaccination. 2 days later Mantoux reaction also flared up. As parenchymal infiltration with large hilar and paravertebral adenitis was discovered upon x-ray and as tuberculous manifestation was established 160 mg streptomycin was injected daily. 1 week later patient developed meningeal symptoms with positive liquor findings. Intralumbar streptomycin application given in addition to intramuscular injections (40 mg daily). Condition

gradually grew worse and patient died despite 4 g streptomycin December 7. In tuberculin test on October 31 Pirquet negative and Mantoux 0.1 mg positive. Clinical diagnosis confirmed by laboratory and bacteriological tests. Post mortem examination not performed at request of parents.

Summary: the first case concerns a girl of 2 years who together with her sisters was exposed to tuberculosis by her father. About 1 week after the onset of the initial fever she was BCG vaccinated following a negative Mantoux 0.1 mg. On the next day she had a high fever reaction, the Mantoux test flared up and Koch's phenomenon was observed at the site of the vaccination. Miliary tuberculosis was discovered roentgenologically shortly afterwards. — The second case was analogous in that a child infected with tb and negative to 0.1 mg Mantoux was vaccinated and strong allergy set in. The course of the disease was malignant in this case also.

Numerous investigators have taken an interest in the influence of BCG vaccination on an incipient or already developed tubercular process. Experience gained through experiments on animals and the vaccination of tuberculous patients has resulted in general agreement that the common doses of BCG vaccine do not affect the course of the disease (LEVITAN, BALANESCO, NEGRÉ and BRETEY, BØE, SORGO, ANTTILA, and others). Large doses seem, however, to be unfavourable for the patient. On that account the subject should not, in principle, be vaccinated when febrile or if the tuberculin test has not been adequate. — In the cases described above the vaccine apparently caused a rise in temperature, but whether or not the prognosis was influenced in other respects is difficult to say. The fact that the disease seemed to take a turn for the worse after BCG vaccination may have been a coincidence. The case given below illustrates this.

Boy, born July 1946. Father had »healed» tuberculosis. Child not tuberculin tested earlier. In February 1947 he had a cough and rise in temperature (considered bronchitis). According to his parents he was quite well later. On May 23 *pertussis vaccination* was performed (suspected incubation) and on the next day he was highly febrile and cramps set in. Admitted May 29 in soporous condition, nystagmus, Kernig

positive. Nonne and Pandy positive in liquor, 28 WBC/mm., no differential count made (Jour-case). Post mortem May 31 revealed *miliary tuberculosis and tb-meningitis.*

Summary

The author studied BCG vaccinated infants at the Children's Clinic of the University of Helsingfors (Prof. A. Ylppö). These children were either suspected of having a tuberculous disease or else a tuberculous disease had already been discovered.

A boy of 7 months vaccinated with BCG shortly after birth died of tuberculous meningitis. Primary tuberculosis or tuberculous pleuritis was found in 6 children. The first tuberculous symptoms were observed from 6 months to 4 years after the vaccination. In 10 cases tuberculous disease was excluded and in 3 cases the tuberculous patients had not been vaccinated with BCG. Furthermore, 3 children infected with tuberculosis had been BCG inoculated after first becoming ill.

The author considers that detailed case records should be published of cases in which BCG vaccinated children have acquired or died of tuberculosis and also of cases of tuberculosis within the non-vaccinated control groups. Such information affords the only means by which an objective opinion may be formed concerning investigations into the prophylactic effect of the method. Attention is drawn to the fact that in certain papers on BCG vaccination the vaccination was performed on already infected persons in the pre-allergic stage. Cases of tuberculosis or suspected tuberculosis in BCG vaccinated children should always be clinically studied. The author points out certain considerations which should be kept in mind (p. 269). In clinical study repeated x-ray examinations of the lungs covering a period of several months are indispensable. A single x-ray picture cannot establish the differential diagnosis between primary tuberculosis and pneumonic processes, or between histoplasmosis and coccidioidosis. The author further stresses the importance of tuberculin sensitivity, the local BCG reaction, and the scar.

Résumé

L'auteur étudie les enfants vaccinés par le B.C.G. à la clinique d'enfants de l'Université de Helsingfors (Prof. A. Ylppö); soit on soupçonnait une maladie tuberculeuse chez ces enfants, soit on avait constaté une telle maladie chez eux.

Un garçon de 7 mois, vacciné par le B.C.G. peu après sa naissance, mourut de méningite tuberculeuse. La primo tuberculose ou la pleurésie tuberculeuse furent constatées chez 6 enfants. Les premiers symptômes de tuberculose furent observés de 6 mois à 4 ans après la vaccination. Dans 10 cas la tuberculose était exclue et dans 3 cas le patient tuberculeux n'avait pas été vacciné par le B.C.G. Trois enfants infectés de tuberculose ont été vaccinés après la maladie initiale.

L'auteur considère que l'on doit publier la description détaillée des cas dans lesquels les enfants vaccinés par le B.C.G. ont été atteints de tuberculose ou sont morts, ainsi que des cas de tuberculose dans le groupe de contrôle non vaccinés. Une telle information est le seul moyen de se former une opinion sur les recherches au sujet de l'effet prophylactique de la méthode. On attire l'attention sur le fait que dans certains documents sur la vaccination B.C.G., dans tous les cas de tuberculose, la vaccination était effectuée sur des personnes déjà infectées à la période préallergique. Les cas de tuberculose constatée, ou de soupçon de tuberculose, chez des enfants vaccinés par le B.C.G., doivent être étudiés en clinique dans ce but. L'auteur indique certains points de vue devant être observés. Dans une étude clinique des radiographies répétées des poumons, durant une période de plusieurs mois, sont indispensables. Une seule radiographie ne peut établir le diagnose différentiel entre une primo-tuberculose et un processus pulmonaire, ou entre une histoplasmose et une coccidiose. En outre, l'auteur souligne l'importance de la sensibilité à la tuberculine, de la réaction locale à B.C.G. et de la cicatrice.

Zusammenfassung

Der Autor studierte BCG vaccinierte Kinder auf der Kinderklinik der Universität Helsingfors (Prof. A. Ylppö). Diese Kinder

waren Tuberkulose-verdächtig oder eine tuberkulöse Erkrankung war bereits festgestellt worden.

Ein sieben Monate alter Knabe, gleich nach der Geburt BCG vacciniert, starb an einer tuberkulösen Meningitis. Primäre Tuberkulose oder tuberkulöse Pleuritis wurde bei 6 Kindern festgestellt. Die ersten Symptome wurden 6 Monate bis 4 Jahre nach der Vaccination beobachtet. In 10 Fällen wurde eine Tuberkuloseerkrankung ausgeschlossen und in 3 Fällen waren die Patienten nicht vacciniert. 3 tuberkulose-infizierte Kinder waren erst nach der Initialerkrankung BCG vacciniert worden.

Der Autor fordert auf, detaillierte Fallverzeichnisse über die Fälle zu veröffentlichen, in welchen BCG vaccinierte Kinder an Tuberkulose erkrankten oder starben, sowie von Tuberkulosefällen bei den nicht vaccinierten Kontrollgruppen. Eine solche Information ist das einzige Mittel, um sich ein objektives Urteil über die Erfahrungen betreffend den prophylaktischen Wert dieser Methode bilden zu können. Beachtung wurde der Tatsache geschenkt, dass in gewissen Arbeiten über die BCG Vaccination, die trotz BCG Vaccination an Tuberkulose erkrankten Fälle solche waren, in welchen die Vaccination bei bereits infizierten Personen im praeallergischen Stadium vorgenommen worden war. Fälle von Tuberkulose oder Tuberkuloseverdacht bei BCG vaccinierten Kindern sollen in dieser Hinsicht klinisch studiert werden. Der Autor weist auf bestimmte Gesichtspunkte hin, welche beachtet werden sollen. Beim klinischen Studium sind wiederholte Röntgenuntersuchungen der Lunge, während einer Periode von mehreren Monaten, unvermeidlich. Ein einziges Röntgenbild kann die Differentialdiagnose zwischen primärer Tuberkulose und einem pneumonischen Prozess oder zwischen Histoplasmosis und Coccidiosis nicht feststellen. Der Autor weist nachdrücklich auf die Wichtigkeit der Tuberkulinempfindlichkeit, der lokalen BCG Reaktion und der Narbe hin.

Resumen

El autor estudia las criaturas vacunadas con BCG en el Hospital de Niños de la Universidad de Helsinki (Prof. A. Ylppö).

Se sospechaba que estos niños tenían una afección tuberculosa o que una afección tuberculosa ya se había manifestado.

Un niño de siete meses, vacunado con BCG poco después del nacimiento, murió de meningitis tuberculosa. Tuberculosis primaria o pleuresía tuberculosa se manifestó en seis niños. Los primeros síntomas tuberculosos se observaron desde seis meses hasta cuatro años después de la vacunación. En diez casos se excluyeron afecciones tuberculosas, y en tres casos no se había vacunado con BCG a los enfermos tuberculosos. Además, tres niños infectados con tuberculosis habían sido inoculados con BCG después de enfermarse inicialmente.

El autor pide que se publiquen informes detallados sobre casos en que niños vacunados con BCG se han enfermado o se han muerto de tuberculosis; también sobre casos de tuberculosis dentro de grupos controlados que no están vacunados. Informaciones de esta clase es el único medio por el cual se puede formar una opinion objetiva de las investigaciones respecto al efecto profiláctico del método. Se llama la atención sobre el hecho que, en ciertos documentos respecto a la vacunación con BCG, todos los casos de tuberculosis, aunque vacunados con BCG, eran aquellos en los cuales se había efectuado la vacunación en personas ya infectadas en el estado pre-alérgico. Por esta razón es necesario estudiar clínicamente los casos de tuberculosis o tuberculosis sospechada en niños vacunados con BCG. El autor expresa ciertos puntos de vista que se deben observar. En un estudio clínico varios exámenes radiográficos repetidos de los pulmones, cubriendo un período de varios meses, son necesarios. Una sola radiografía no puede establecer la diagnosis diferencial entre tuberculosis primaria y procesos nemónicos, o entre histoplamosis y coccidiosis. El autor recalca además la importancia de la sensibilidad tuberculínica, la reacción local de BCG y la cicatriz.

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FROM THE BLEGDAM EPIDEMIC HOSPITAL, COPENHAGEN (CHIEF: PROFESSOR H. C. A. LASSEN, M. D.), AND THE PEDIATRIC DEP'T OF THE RIGSHOSPITAL, COPENHAGEN (CHIEF: PROFESSOR P. PLUM, M. D.)

Dermatomyositis in Children

by

HANS SUNDE

About 1887, WAGNER, HEPP, and UNVERRICHT described independently of each other the clinical picture which UNVERRICHT in 1891 designated *dermatomyositis*. WAGNER and other authors have called the lesion polymyositis. HEPP suggested calling it pseudotrichinosis.

For a review of previous cases the reader is referred to STRÜMPELL (1), who in 1891 gave a detailed survey of the first cases published; STEINER (2), who in 1904 collected 28 cases and gave a comprehensive list of literature; and KARELITZ & WELT (3), who in 1932 gathered 75 cases, 22 of which occurred in children. SCHUERMANN (4) found 263 cases reported in the literature up to 1938, and O'LEARY & WAISMAN (5) described 40 cases admitted to the Mayo Clinic from 1926 to 1939.

In the Scandinavian countries, most cases have been published from Denmark, some from Sweden, and a few from Norway.

The disease appears to be distributed evenly throughout the world, having been described in Japan, Russia and other European countries, and the U. S. A. It seems to have no particular relationship to sex or race. The age distribution curve rises abruptly at the age of 3 years and reaches its maximum in the 2'—3' decade, whereafter it falls slowly (SCHUERMANN (4)). It is a rare disease, though presumably more frequent than has previously been assumed.

The symptoms are many and very variable. The course may be acute, subacute or chronic, and the etiology is still obscure.

In typical cases the diagnosis may be made clinically, but biopsy of the muscle and possibly of the skin, too, should always be performed. The skin changes may be rather inconspicuous or entirely absent, on which account the original term »polymyositis» may still be seen in the literature. As will be mentioned later, in recent years several authors have claimed that other morbid conditions should also be classified under the same nosological entity.

As the present two cases supplement each other and show most of the symptoms pertaining to this lesion, it will be appropriate to describe them at some length here prior to a general survey of the symptomatology.

Case 1[1]

The patient was a ten-year-old boy born in 1937 four weeks before term. His birth weight was 2 250 g. Apart from uncomplicated measles in 1939 and chickenpox in 1942, his health was excellent until the summer of 1944, when he commenced to have attacks of rigidity and numbness of the fingers. The stiffness increased gradually. At first it involved only the wrist and finger joints, but gradually it extended also to the knees, ankles and hips, so that walking became difficult and his gait slow and dragging like that of an old man. Finally, he had to be helped in dressing and undressing.

On March 26, 1945, he was admitted to the Pediatric Department of the Aarhus City Hospital for trophic disturbances of the nervous or muscular system. Here he was treated with sanocrysin, as he was thought to have incipient chronic polyarthritis. Altogether he was given 88 cg. sanocrysin intravenously in 8 injections. Adenotomy was performed and physiotherapy given.

Four days after the last sanocrysin injection he became febrile, his temperature remaining at about 39° for a week. At the same time he had tonsillitis and (4 days later), a non-characteristic exanthema which persisted for 5 days. Clinically there was reduced mobility of the wrist and finger joints together with swelling of the wrists. The findings in laboratory examinations at this time may be summarized briefly as follows.

Hemoglobin 90 %; white blood count about 7 500. Differential

[1] Reported before the Danish Society of Pediatrics on Sept. 24, 1947, by S. Brandt.

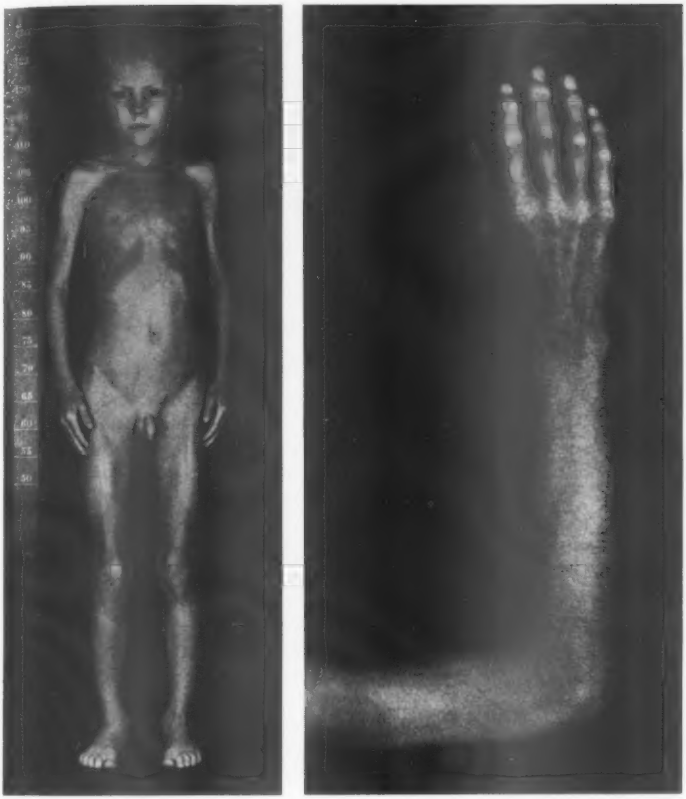

Fig. 1. Case 1. Photo taken on Sept. 1, 1947.

count: 0—23 % eosinophils, most often 6—10 %, also increased before sanocrysin therapy; otherwise no abnormal findings. Sedimentation rate: 4—23—6 mm/1 hr. Antistreptolysin titer (AST): 56—64 (*i. e.*, normal values). Urine: no abnormality; after sanocrysin treatment a few formed elements, including granular casts. Feces: +eggs of worms. Tuberculin test and Widal test negative. Roentgenography of joints: no abnormality. Electrocardiography: normal.

Discharged from the hospital on May 30, 1945.

Follow-up exam. in August/September: joint pains or steady elevation of temperature never noticed. No skin eruption since discharge. Mobility somewhat improved.

During the following 2 years the child's condition gradually became worse, and 2 months before admission to the Pediatric Dep't of the Rigshospital, Copenhagen he was almost unable to walk and had to be assisted in dressing and undressing. The pains were confined chiefly to the thighs, as if the muscles were overexerted.

On September, 1947, he was admitted to the Pediatric Dep't of the Rigshospital. His record there reads as follows:

Boy, 10 years old, of almost normal height, and nearly 6 kg underweight. Height 130 cm. Weight 25 kg.

Over almost the entire chest and extremities the skin was markedly atrophic, glossy, light-reflecting, and tight, especially over the wrist, knee and ankle joints. Subcutaneous veins were distinctly visible through the epidermis. The lanugo was practically normal. The palms were slightly hyperemic and moist. The boy's face was pale and rather expressionless; the facial skin was somewhat fuller, but firmer and less elastic than normal. The upper eyelids showed a fine network of small blood vessels suggestive of telangiectasis. Something similar was seen over the patellae and malleoli, where the skin was particularly thin. The ears looked stiff, with tight glossy skin.

No nodules or thickening of the skin was felt anywhere along the palpable arteries.

The musculature was universally atrophic, somewhat firmer than normal, and without tenderness, palpable infiltrations or soft parts. The boy's muscular power was good. His tendon reflexes were lively.

There was considerable reduction of the mobility in the wrist, ankle, and hip joints, moderate reduction in the knee and finger joints, and only slight reduction in the mandibular, shoulder and elbow joints. The hands could not clench fully. There was no swelling of the joints but atrophy and shrinkage of connective tissue around the stiffened joint. Universal enlargement of the peripheral lymph nodes and large, pitted tonsils were noted. There was caries of 4 milk teeth.

Physical examination showed otherwise normal conditions.

Laboratory examinations: hemoglobin: 70—90 %. Colour index: < 1. White blood count: 8 500—12 500. Thrombocytes: 174 000. Capillary resistance normal. Differential count: normal (in particular, no eosinophilia). Sternal bone marrow: no abnormality (eosinophils 3.8 %, plasma cells 1 %). Serum protein: total 8.9—7.1 %; albumin 4.3—3.9 %; globulin 4.6—3.2 %. Serum cholesterol 195 mg%. Sedimentation rate: 3—23—4 mm/1 hr. AST: 100—100—800; the last value obtained in February, 1948, two months after acute tonsillitis. Throat culture. Nov.—Dec., 1947: +hemolytic streptoccocci, Group A, type 1. Other-

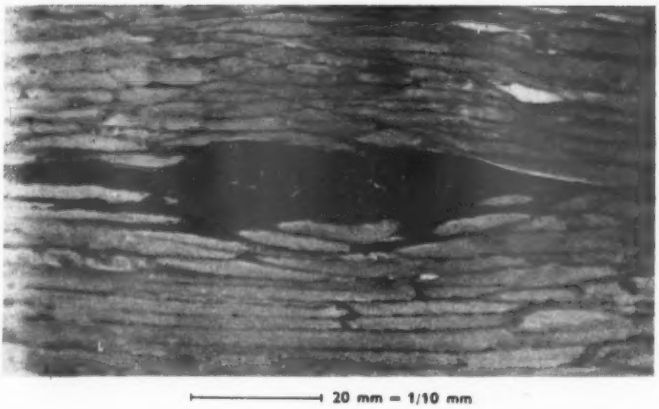

Fig. 2. Case 1. Microphoto of m. vastus lat. Magnif. ×200.

wise no growth of hemolytic streptococci in several cultures. Streptococcus agglutinin titer: 40—0. Urine: no abnormal elements. Ophthalmoscopy: no abnormality. Electrocardiography: no abnormality. Tuberculin test negative. Wassermann negative. Serum calcium: 8.5—10.6 mg%. Blood phosphorus: 3.2—4.5 mg %. Phosphatase: 68—170 units (Lundsteen & Vermehren). Roentgenography: Halisteresis of the long bones, otherwise normal findings (no abnormalities in the thorax, dentes and sinus). Capillary microscopy (sept. 1947): the capillaries in the mantle of the nail were strikingly few and markedly tortuous, with thin afferent ("arterial") and dilated efferent ("venous") parts.

The creatine excretion with the urine was examined twice in September, 1947. The 24-hour output was:

creatine: 190—130 mg, or 8—5.3 mg per kg. body weight;
creatinine: 480—640 mg, or 20.5—26 mg per kg body weight.

These values cannot be taken as definitely pathological.

The diagnosis of dermatomyositis was made clinically in collaboration with dermatologist and specialist in physical medicine; subsequently it was verified by skin and muscle biopsy, which showed the following:

> Sections from the skin showed a few areas where blood vessels were surrounded by moderate infiltration with lymphocytes. In a few places such infiltrations were also seen in the subcutaneous fatty tissue. Otherwise there were no definite abnormalities.

Sections of muscle showed rather large infiltrations with lymphocytes in the muscular interstices and also in the surrounding fatty tissue. There were a few plasma cells and some histiocytes. Here, too, the inflammatory infiltrations were not infrequently located around vessels. In most areas the muscle fibrils appeared normal, but in some places the striation was rather inconspicuous and the contours irregular. In a few places both the longitudinal and transversal striation had disappeared and the fibrils were wavy and irregular.

Histological diagnosis: dermatomyositis.

(Signed: Eskelund.)

Thus the clinical diagnosis was fully established by the typical pathologic-anatomical findings.

The patient was suffering from a disease of inflammatory, but not suppurative, character, localized at any rate to the subcutaneous tissue and underlying musculature. The almost universal extent of the atrophy of the skin indicated that these changes were very extensive.

The boy received penicillin treatment for 5 weeks (80 000 O.U. × 3—altogether 7.7 million O.U.) and physiotheraphy. His condition improved functionally. But there was no definite improvement in the digital contractures (May 1948).

On October 14, 1948 he was readmitted to the Pediatric Dep't of the Rigshospital, where he still is at this writing.

At home he was given ambulant treatment with baths and physiurgic therapy, but the contractures increased universally.

Since 10/16 he has been treated with baths and active and passive motions every other day. Since 11/16 niglin ointment (2 % nitroglycerin in an easily absorbable ointment base) has been applied to his right hand twice a day. Under this treatment the hand has been feeling warmer, but there is no essential improvement of the scleroderma. Since 11/24 he has received penicillin (240 000 O.U. daily) injected intramuscularily. Under this treatment the contractures have improved a little.

The more important laboratory findings are as follows: Hemoglobin 100—80 %. Sedimentation rate (Westergren) in Oct. and Nov.: 10 mm/1 h.

AST: 110—140 (*i.e.*, slightly increased).

Streptococcus agglutinin titer: 160 (*i.e.*, slightly increased).

Creatine excretion per day (after meat-free diet for 3 days): 230 mg. or 9 mg per kg body weight (*i.e.*, slightly increased).

Capillary microscopy in December: practically the same features as found in September, 1947 (cf. Fig. 4).

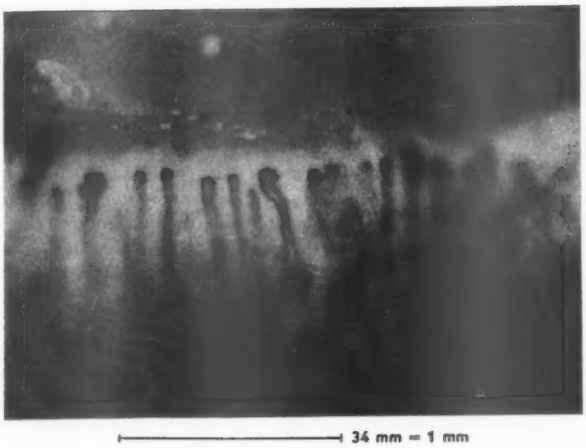

Fig. 3. Normal adult. Microphoto of capillaries in mantle of the nail. (Magnif. × 34.)[1]

Fig. 4. Case 1. Microphoto of mantle of the nail. Only few and markedly tortuous capillary loops with thin »arterioles» and dilated »venules». (Magnif. × 34.)

[1] Microphotos for Figs. 3, 4 were obligingly taken by Professor P. Brandt Rehberg, Ph. D. in the Zoophysiological Laboratory of the University of Copenhagen.

Case 2[1]

The patient was a girl 11 years old, born at term by normal delivery. The family history was negative apart from a slight tendency to urticaria in the other children. The patient had urticaria herself after fairly large doses of cod liver oil, but otherwise she showed no signs of allergic affections.

Apart from frequent tonsillitis from early childhood, she was well till the age of 5 years when she had a primary tuberculous affection that took a mild course. Subsequent repeated roentgenography of the lungs has shown complete healing. At the age of 10 she was admitted to the Blegdam Hospital with scarlet fever. Throat cultures showed growth of hemolytic streptococci, Group A, type 8, and she was given penicillin (80 000 O.U. × 3 daily for 6 days). The course was uncomplicated, and AST did not rise over 200, subsiding again after 3 weeks.

In the beginning of June, 1947, she fell off her bicycle and had a few small excoriations on the left foot, knee and hand. Two days later there was a red, slightly elevated spot resembling an insect bite on the left thigh. Gradually she began to feel poorly and became febrile, when the skin eruption spread to the right thigh and both arms. It was accompanied by general soreness, more pronounced at the eruptions and excoriations.

On admission five days after the onset of the disease the patient was markedly exhausted. Temperature 39.8°. Redness and slight swelling of the tonsils, gingivitis and coated tongue, besides tenderness round the left wrist joint and edema of the dorsum of the hand.

The exanthema spread in the form of roundish, slightly elevated, tender, infiltrated spots with a slightly bluish red center and a brighter red marginal zone. It was strongly suggestive of erythema nodosum. The elements gradually became confluent, suggesting erythema multiforme, which at first the affection was taken to be. On the fourth day after admission there was distinct edema of the face, especially round the eyes, where the skin gradually took on a peculiar bluish-red color. Edema also developed on the arms and legs, in some places distinctly subfascially as well. There was tenderness on palpation of the muscles and several small spots on the palms and soles. At the same time there appeared a transitory hoarseness and difficulty in mastication and deglutition.

At this stage the diagnosis of dermatomyositis was assumed. It was clinically confirmed following examination by a dermatologist about two weeks after the onset of the disease.

To simplify perception of the course of the disease the more important examinations showing deviations from the normal are recorded in Fig. 5, which also shows most of the treatments.

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[1] Reported before the Danish Society of Pediatrics on Nov. 2, 1947, by the author.

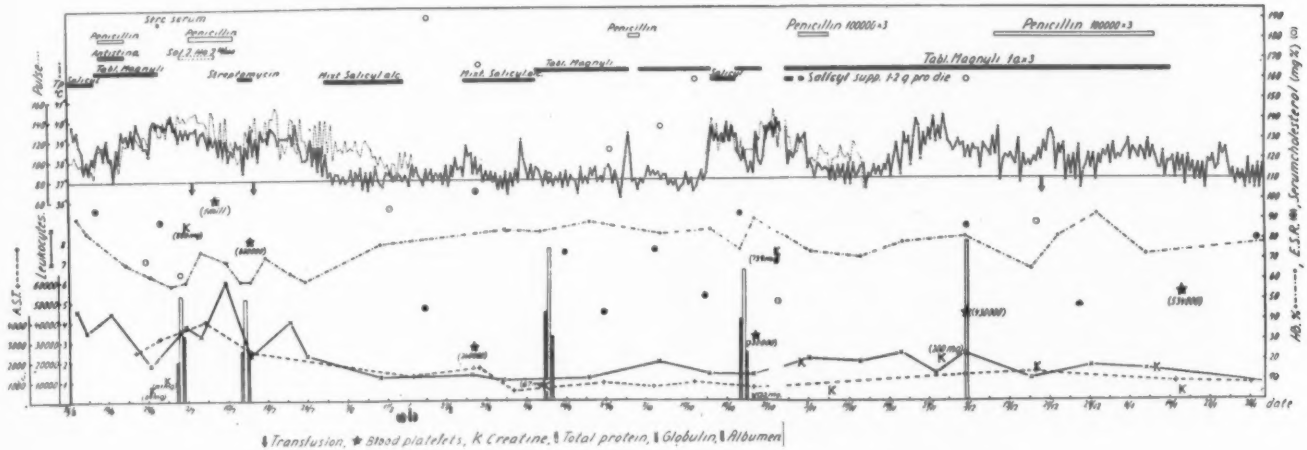

Fig. 5. Case 2. Graphic presentation of clinical data and laboratory findings (see the text).

Fig. 6. Case 2. Photo taken in latter part of June 1947.

As is evident from Fig. 5, during the first two weeks the temperature was irregular, varying between 37° and 40°. The sedimentation rate was increased. The white blood count was increased, and the hemoglobin percentage decreasing.

At first treatment consisted of peroral administration of sodium salicylate in slightly alkaline solution (2.5 g daily). Then acetylsalicylic acid with magnesia was given (2 g daily). At times salicylate appeared to have a favourable effect, at any rate symptomatically, mitigating the pain and lowering the fever. As it was assumed that the child's affection possibly might be allergic in type, an antihistamine preparation (antistina) was tried, but without any effect. For a time she was also given penicillin (60 000 O.U. × 3 daily), as her condition was somewhat suggestive of sepsis. As this appeared to have no effect it was discontinued after 5 days, but later on repeated in larger dosage. Streptomycin ($\frac{1}{2}$ g × 3 daily) was given only for 3 days (cf. Fig. 5).

Important for the diagnosis was increasing muscular tenderness, edema and the fairly characteristic exanthema (Figs. 6 & 7).

Fig. 7. Case 2. Photos taken on July 3, 1947.

Biopsy of the muscle at this juncture showed relatively slight changes which will be mentioned later in the summary of the examinations.

The further course of the disease was characterized chiefly by spontaneous remissions and exacerbations. After the first two weeks when her temperature varied somewhat, she had a high fever for about one month, together with anemia — in spite of 2 blood transfusions of 500 ml citrated blood. As the peripheral veins were filling strikingly poorly,

the second transfusion was given intrasternally. The hemoglobin value was raised only temporarily but the edemata subsided and the exanthema became more conspicuous. New spots of the same appearance turned up steadily — among other places, a tender blue spot appeared on the tongue — while the ears became more diffusely red and tender.

The child's general condition kept growing worse. Finally she was lying listless and apathetic with joints semiflexed, moaning at the least movement or even at a light touch. She also had nausea and vomiting and there was involuntary passage of the urine.

In order to counteract the development of contractures, adhesive tape extension was applied to the lower extremities; but when she had symptoms of thrombosis in the right leg the extension was removed again and she was given "Synparin" (dicumarol). During this treatment the prothrombin time was not examined, and she had symptoms of hemorrhagic diathesis: first a hematoma of the right labium majus; shortly after, clinical features resembling peritonitis. There were also transitory hematuria and epistaxis. "Synparin" was discontinued at once, but at this juncture she was almost moribund. She was given large quantities analgetics in the form of morphine preparations.

After about one week she improved rapidly, so morphine was discontinued, and salicylic mixture given again. There was a lytic fall in temperature but the pulse rate was still relatively high (see Fig. 5).

Subsequently she had two brief periods with scattered spots of the same exanthema and slight elevation of temperature.

In order to counteract contractures, she was placed for a while in a plaster cast at night. During this period she complained for 2—3 days of a strong sensation of cold in the left hand and foot, which also objectively felt strikingly cool, while the temperature was normal on the right side.

Under physical treatment together with salt baths she improved so much in the course of 3—4 weeks that she was able to get up and walk with support. She was gaining 400—500 g a week.

In the last week of September, 1947, she had an acute attack of tonsillitis. Throat cultures showed growth of hemolytic streptococci, Group A, type X — *i.e.*, indeterminable type — and she was treated with penicillin for 2 days (150 000 O.U. × 2). Subsequent throat cultures at first turned out negative, but later showed sporadic hemolytic streptococci (Group A, type X).

Two weeks after the attack of tonsillitis she had a dermatomyositis relapse with repetition of all the previous symptoms excepting thrombosis and abdominalia; and now there was a distinct diffuse alopecia. During this relapse she was less exhausted than before. One of the spots on the leg showed fluctuation and puncture gave a greyish-yellow granu-

lar viscous fluid which in cultures yielded no bacterial growth (also anaerobically). No chemical analysis of the fluid was made.

From the middle of January, 1948, she was much better, apart from several exanthema relapses, sometimes with slight elevation of the temperature. She improved gradually and was now gaining little weight. She was again given physical treatment, and this time it took a little longer before she was able to walk. The muscular atrophy had become considerable, and on commencing to walk there was a slight accumulation of fluid in both ankles, besides pain on motion. As remnants of the exanthema there were still a couple of fairly firm infiltrations, but no definite calcification. Pigmentation was marked on both feet, slight on legs and arms.

In the middle of March, 1948, she was able to walk well without support; and there was a distinct improvement in the muscular atrophy. She was discharged from the hospital.

Laboratory Examinations (see Fig. 5):

As will be noticed from the lower part of Fig. 5, several findings deviated from the normal.

Hemoglobin: 92—58—90—65—102 %. Erythrocytes: 4.29—2.6—4.10—3.29—4.5 millions. Colour index from 0.94 to 1.14, most often about 1.

White blood count (full line) varying from 10 000 to 60 000. Differential count: slight shift to the left in Arneth's blood picture and toxic granulation; no eosinophils on admission, 5 % at discharge. Sternal bone marrow, 6/14/47, hyperplastic with increase in plasma cells (6.5 %); otherwise no abnormalities.

Thrombocytes (in Fig. 5 recorded under asterisk): 1 000 000—263 000.

Bleeding time, clotting time, capillary resistance, and prothrombin time (not examined regularly): no abnormality.

Blood group: A, Rh-positive.

Serum protein (cf. columns in Fig. 5): total protein 5.3—5.1—7.6; albumin: 2—2.5—4.4 %; globulin: 3.3—2.6—3.2 %.

Fibrinogen: 0.82—0.72 %.

Serum cholesterol (indicated by circle in Fig. 5): mostly low values; in the febrile period: 49—190 mg%.

Basal metabolism: 103 %. Weight: 24.6—26 kg. Height: 142 cm.

Sedimentation rate (recorded as black dot) greatly varying: 96—46—104—44—102—11—5 mm/h.

AST (lower broken line in Fig. 5), 2 weeks after onset: 2 500 (normal maximum 100—200), rising rapidly to 4 000, then varying from 500 to 1 400 synchronously with relapse of exanthema and fever; finally subsiding slowly, and on last examination (in middle of Aug. 1948) 160.

Streptococcus agglutinin titer: O. Tetanus antitoxin: $\leqq 0.0001$ U.

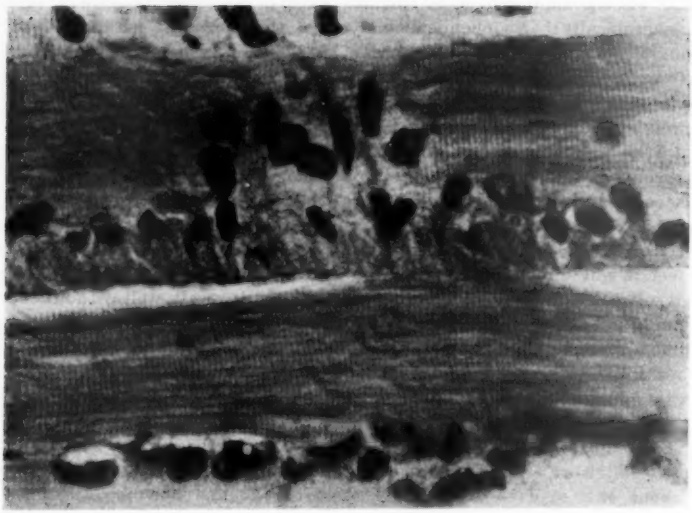

Fig. 8. Case 2. Microphoto of m. vastus lat. Magnif. ×1000.

Staphylococcus antitoxin: < 2 (*i.e.*, not increased). Repeated blood cultures showed no bacterial growth. Electrocardiogram normal throughout stay in the hospital. Urine: slight albuminuria in the first 3 weeks. Test for Bence-Jones protein negative. Casts observed once when she was very ill. Transitory hematuria once. Otherwise normal findings. No porfyrinuria.

Creatinuria (indicated by K in Fig. 5): only twice was the creatine output found to be pathologically increased, both times in periods with fever and without administration of salicylate. These two times it was 880 and 739 mg% respectively, which corresponds to about 34 and 28 mg per kg of body weight.

Muscle biopsy (m. vastus lat.) performed by dr. Bj. Vimtrup: only a few areas showed degenerative changes, blurring of striation, somewhat wavy and curly muscle fibers, and a striking increase in the number of sarcolemnic nuclei, besides some irregularity in the thickness and stainability of the fibres. The interstitial blood vessels showed but few leukocytes; the endothelium may possibly have been slightly swollen. No sign of trichinosis.

Diagnosis: Myositis.

Roentgenography of extremities and chest, on admission: no abnormality.

Laboratory findings: Serum calcium (several times): normal values. Tuberculin test: on admission Moro's test negative. Later Mantoux strongly positive. Gastric lavage: ÷ T.B. Ewald testmeal: 21 cc; free acid 41; total acidity 69. Of the other examinations that turned out negative the following should be mentioned for the sake of completeness: benzidine test on feces, Widal, Paul-Bunnell, cold-agglutination, formolgel, thymol, and precipitin reaction for trichinosis. Ophthalmoscopy: eye-grounds normal. Neurologic examination: normal findings. Electromyography: no definite abnormality.

On intracutaneous titration on rabbits, no toxoplasm-neutralizing antibody could be demonstrated by employment of the human strain Rh. (Dr. J. Chr. Siim).

Reexaminations (nearly every month):

In the course of April and May the patient improved considerably, so that in June she was able to walk normally, ride her bicycle and go roller-skating.

The left fingers were a little thin and weak compared with the right and the musculature of the hands was slightly atrophic. Otherwise there was no noticeable muscular atrophy.

The pigmentation of the skin after the exanthema subsided, and no definite areas of calcification or atrophy in the skin appeared.

Weight in May, 1948: 30 kg; August: 33 kg.

December 1948: *Muscle biopsy* (forearm) in connection with skin excision for "cosmetic" reasons showed perfectly normal muscle tissue (Dr. Erna Christensen).

Capillary microscopy, December, 1948: a few areas with slightly tortuous and dilated capillary loops, rather scattered, but otherwise practically normal.

The symptomatology has been thoroughly dealt with by several previous authors, in particular O'LEARY & WAISMAN (5).

Several authors mention a prodromal stage with greatly varying symptoms. SCHUERMANN (4) and others assert that here we are dealing with a lesion that appears secondarily to various infectious diseases. This will be discussed later.

In order to give a brief survey of the character and frequency of the various symptoms, it may be appropriate to tabulate in outline form the symptoms encountered in 40 cases admitted to the Mayo Clinic (O'LEARY & WAISMAN (5)).

Table 1.

Incidence of Various Symptoms in 40 Cases of Dermatomyositis from the Mayo Clinic (O'Leary & Waisman[5]).

Signs and Symptoms	No. of Cases
Anemia — in practically every case	(40)
Skin symptoms	38
Muscle pain and weakness (in 18 cases the first symptom)	34
Vasomotor disturbances (in 2 cases prior to skin changes)	rather common
» symptoms of type acrocyanosis and Raynaud's disease in	10
Periorbital edema (in 1/3 from the beginning)	25
Lack of facial expression	very common
Dysphagia	25
Albuminuria (slight)	14
Hoarseness	13
Scleroderma (moderate, with pigmentation in 5 cases)	12
Fever, not over 39°	11
Eosinophilia (moderate)	11
Dyspnea, considerable	10
Sedimentation rate increased	9
Stomatitis	9
Pigmentation of skin (with scleroderma in 5 cases)	9
Enlargement of the spleen (slight)	8
Alopecia, diffuse	7
Tremor of the tongue	6
Calcified nodules in subcutis	5
Enlargement of the liver (palpable)	5
Enlargement of the heart (moderate)	5
Electrocardiogram abnormal	4
Diplopia	4
Casts in the urine	4
Sphincterial insufficiency (anal 3, vesical 1)	4
Enlargement of lymph nodes (moderate)	3
Myocardial changes (found on autopsy)	2
Areas of calcification in soft parts of pelvis (demonstrated roentgenologically)	1

Ophthalmoscopy performed in 30 of these 40 cases showed no abnormality.

Changes in the eye-ball have been described but are so rare that they should perhaps be looked upon as accidental findings. Iritis is reported by OPPENHEIM (cited after SCHUERMANN (4)). Retinopathy is described in 3 cases, the last one by LISMAN (10).

OPPENHEIM (11) was the first to describe mucosal changes in dermatomyositis. Besides stomatitis and gingivitis in the initial stage, there may be enanthema similar in appearance to the exanthema.

The exanthema is somewhat variable but usually consists of slightly elevated spots, roundish, tender and infiltrated and crimson in color. It may be morbilliformly confluent, however, or somewhat streaky. The individual elements vary greatly in size and they are most frequently distributed over the areas exposed to light, often round the joints on the extension aspect, now and then in the palms and on the soles — here usually as quite small elements.

The muscular changes consist of decrease in power, stiffness and tenderness, with pricking pains on motion. On palpation the muscles feel indurated, with a few more tender areas here and there. Usually the laryngea, pharyngea and respiratory muscles are not attacked till late in the disease.

The edemata are usually localized to the extremities and the face; they are partly subcutaneous and partly subfascial, and may be very pronounced. Periorbital edema with bluish-red skin colour is particularly characteristic.

Pronounced atrophy of the musculature and skin is seen in chronic cases.

The vascular changes include strikingly poor filling (»emptiness») of the peripheral veins, while the capillaries are congested and tortuous (*e.g.*, STRÜMPELL (1), SCHUERMANN (4), and HECHT (12)). Also, several cases have been reported with more serious circulatory disturbances, and the differential diagnosis from thrombangitis obliterans and periarteritis nodosa is mentioned by, among others, SILVERMANN & POWELL (13).

Pathologic-anatomical changes are found as described in Case 1 by several previous authors (*e.g.*, FREUDENTHAL (14)).

Discussion

More recent authors appear to agree that sclerodermia, universal calcinosis and dermatomyositis constitute a nosological unity — as discussed in detail by HECHT (12) and others. This view is based on clinical and anatomical features. Even lupus erythematosus disseminatus, the Libman-Sacks syndrome and periarteritis nodosa have possibly a common denominator — as suggested by BANKS (15). Some authors have also compared the dermatomyositis to thyrotoxicosis and myasthenia gravis — on account of points of resemblance in the pathologic-anatomical changes (DOWLING & GRIFFITHS (16)).

As the etiology still is obscure, all possibilities have been discussed in the course of time. Theories about connection with endocrine disturbances find only slight support; besides thyrotoxicosis, connection with pregnancy has been emphasized, and some cases have been described in which ovarian tumors were present at the same time. Relatively many cases have been seen in connection with malignant tumors of various types and localization. Here it may be mentioned that JØRGENSEN (17) has described a case of plasmocytoma with symptoms like those found in dermatomyositis.

The theory of an infectious origin has been advanced in particular. In spite of very thorough search for bacteria and viruses, however, the results have been either negative or rather conflicting. The same applies to examinations for parasites. Various avitaminoses have been suggested but no longer find support (cf. CHRISTENSEN & REMVIG (6)).

As early as 1891 BOECK (9) suggested that the cause might be found in peripheral vascular disturbances of central nervous origin, and he reported a case which he thought was cured with acetanilid.

SCHUERMANN (4) arrives at the conclusion that the pathogenesis may be a vascular lesion with symptoms from the peripheral circulation. He looks upon the affection as a protracted state of collapse.

Considering the two cases reported here, we find that in Case

1 the onset was insidious, without demonstrable prodromata, and that the disease took a chronic course. Here the resemblance of the clinical picture to sclerodermia was conspicuous. Indeed, the writer thinks that no sharp distinction may be made between these two lesions (cf. HECHT (12) and BANKS (15)).

In Case 2 we meet with a pronounced acute onset which strikingly suggests that of an infectious disease. There is relapsing angina, which several authors emphasize as frequent in these patients. The course is violent, with exacerbations and remissions and distinct vascular symptoms. The antistreptolysin titer, strikingly high early in the disease and varying throughout its course is suggestive of streptococci as a causal factor. It is significant that penicillin showed no definite effect, however.

Thus we arrive at the question whether dermatomyositis is a primary or secondary affection. This is discussed thoroughly by SCHUERMANN (4), who after study of the reports in the literature thinks he has found that in most cases dermatomyositis may be shown to appear in connection with a number of lesions, chiefly infectious diseases among which the following may be mentioned: tonsillitis, sinusitis, influenza, scarlet fever, measles, whooping cough, rheumatic fever, rheumatic polyarthritis and tuberculosis. He also mentions gonorrhea, gastro-intestinal infections and intoxications.

So it seems possible that dermatomyositis represents a morbid condition with hypersensitiveness of the skin and muscles to a circulating antigen or bacterial product. Several things might be taken to indicate that this is not specific. On the other hand, it may be pointed out that in the literature streptococcus infections are mentioned as constituting a very frequent complication, even though few authors recognize them as an etiological factor. Here it should be mentioned that HOLST (7) has described 5 cases of dermatomyositis or sclerodermia, 4 of which showed increased AST — a test that in many cases has been neglected.

Obviously the treatment has to be symptomatic. Generally chemotherapy has proved ineffective. Still, CLARK (18) has described a case which he thinks was cured with penicillin. However this may be, penicillin ought to be employed in cases with

recurrent angina, and protection against infections must be considered an important part of the treatment.

Further, salt baths, gymnastic exercise, and, in severe cases, correction of contractures are essential therapeutic measures. In our Case 2 salicylate seemed to have had a favourable effect in febrile periods.

The prognosis varies with the age of the patient. According to SCHUERMANN (4), in patients under 30 years, the death rate is a little under 50 %, but after thirty it increases rapidly. The course varies greatly, and the disease may last from a few months to some years, the chief cause of death being intercurrent infections, especially with streptococci or pneumococci. Of the patients who recover, many have permanent skin changes or contractures, the chances of complete recovery seem much greater in the younger age groups, especially children, than in adults.

Summary

Two instances of dermatomyositis in children show the more important symptoms, with an acute remittent course in one case and a chronic course in the other.

Noting definite can be said about the etiology, but attention is called to streptococcus infection. Strikingly many cases appear to show increased antistreptolysin titers.

It is discussed whether dermatomyositis may be looked upon as secondary to certain infectious diseases, possibly a state of hypersensitiveness of the skin and muscles to some circulating antigen or bacterial product.

The treatment is symptomatic. Protection against infections during the course of the disease is important.

Résumé

Deux cas de dermatomyosite chez des enfants montrent les symptômes les plus importants, avec un cours aigu rémittent dans un cas et un cours chronique dans l'autre.

Rien de définitif ne peut être dit au sujet de l'étiologie, mais

on attire l'attention sur l'infection par streptocoques. Un nombre remarquable de cas semblent montrer une croissance de titre d'antistreptolysin.

On se demande si la dermatomyosite peut être considérée comme une maladie secondaire de certaines maladies infectieuses, peut-être une forme d'hypersensibilité de la peau et des muscles à quelque produit antigène ou bactérien ambulant.

Le traitement est symptômatique. Il importe de protéger le malade contre les infections durant le cours de la maladie.

Zusammenfassung

2 Beispiele von Dermatomyositis bei Kindern zeigen die wichtigsten Symptome mit akut remittierendem Verlauf in dem einen und chronischem in dem andern Falle.

Über die Ätiologie kann nichts Definitives gesagt werden, es wurde aber die Aufmerksamkeit auf eine Streptokokken-Infektion gerichtet. Auffallend viele Fälle scheinen einen erhöhten Antistreptokokkentiter zu zeigen.

Es wird erörtert, ob die Dermatomyositis als sekundär nach bestimmten Infektionskrankheiten, möglicherweise als ein Zustand von Überempfindlichkeit der Haut und der Muskeln gegen irgendein zirkulierendes Antigen oder Bakterienprodukt angesehen werden kann.

Die Behandlung ist symptomatisch. Schutz vor Infektionen während des Krankheitsverlaufes ist wichtig.

Resumen

Dos ejemplos de dermatomiositis infantil muestran los síntomas importantes con un curso agudamente remitente en un caso y crónico en el otro.

No se puede decir nada definitivo en lo que se refiere a la etiología, pero se llama la atención sobre una infección estreptocócica. Es notable que muchos casos parecen demostrar un título aumentado de antiestreptolisina.

Se discute si se puede considerar la dermatomiositis como secundaria a ciertas enfermedades infecciosas, posiblemente un

estado de hipersensibilidad de la epidermis y de los músculos con relación a algún producto circulatorio antígeno o bactérico.

El tratamiento es sintomático. La protección contra infecciones durante el curso de la enfermedad es importante.

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Addendum

Before printing this paper some further particulars about Case 2 may be added here.

On May 27th 1949 the patient was admitted to the neurological Dept. of the Kommunehospital, Copenhagen, with a slight bitemporal hemiamblyopia, discovered on routine examination at the school. By operation at the neurosurgical Dept. of the University Clinic in Copenhagen (7/25–1949) a mostly suprasellar tumor was completely excised and microscopical examination showed the picture of a chromophobe adenoma of the hypophysis. By kind permission of Professor A. Busch the roentgenograms of the skull and of arteriography was inspected by the author and they may be said to indicate the existence of the tumor at the time she was suffering from Dermatomyositis.

FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT KRON-PRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM.
(HEAD: PROFESSOR A. LICHTENSTEIN.)

Fat Resorption in Congenital Cystic Fibrosis of the Pancreas in a Child Aged 6 Months

by

IB BOESEN, Copenhagen

Experiments with qualitative and quantitative fat resorption in congenital cystic fibrosis of the pancreas have only been carried out in a few cases in children under 6 months of age. Hence it seems worthfully to publish the present report, on fat resorption in a case of pancreatic cystic fibrosis verified at autopsy in a child aged 6 months.

The patient was born Aug. 17. 1947, the fourth of 4 children. Both parents were healthy and the mother presented no symptoms of illness during pregnancy. A sister 8 years old and a brother 5 1/2 years old are well. A brother was born in 1945. At the age of 6 weeks he contracted a capillary bronchitis for which he was admitted to Norrtull Children's Hospital where he died of pneumonia 3 weeks later. The autopsy diagnoses were bronchitis and acute lobar pneumonia; patent ductus arteriosus. Gross examination of the pancreas was negative. No microscopic examination was made of the organs. In addition to the above-mentioned pregnancies the mother had had two miscarriages, viz. May 1944, in the second month, and October, 1946, in the third month.

The patient was born at full term; delivery was normal. Her birthweight was 3 550 g. She was exclusively breast-fed during the first month and thereafter breast-fed with various supplements until she was 4 months old, when the mother's milk secretion ceased. In the period immediately after birth the patient lost 500 g but thereafter she gained satisfactorily the first month.

She then began to cough. Gradually the cough assumed the character of bouts of whooping cough, associated with vomiting. As the patient failed to gain weight despite supplements consisting of citric acid milk and human milk, medical advice was obtained at the medical outpatient department of Crown Princess Lovisa's Children's Hospital in October, when the patient was 2 months old. Her weight was then 4 030 g. X-ray examination of the lungs showed a consolidation the size of a plum in the right middle lobe. Mantoux's test gave 10 × 10 mm (received BCG vaccine at birth). Human milk was prescribed as a supplement to the mother's milk, and the patient slowly gained weight, reaching 4 160 g in the course of a month. When a little less than 5 months of age the patient developed chickenpox (in January, 1948) and in connection therewith suffered another attack of pneumonia. She was acutely ill and lost weight. Up to December her stools had been of almost normal appearance, but after that time they became large, grayish-white and foul-smelling.

On account of her poor condition following pneumonia the patient was admitted to the Crown Princess Lovisa's Children's Hospital, medical department (141/48) at the beginning of February, aged 5 1/2 months.

Examination on admission showed an extremely emaciated child of typically atrophic appearance, with slender limbs and large abdomen. Her weight was 4 030 g. Her psychical development was considered to be normal for her age, and she could discern objects and was interested in what happened around her. She had protracted and severe pertussis-like bouts of coughing in connection with which there were vomits, so large that on some days she vomited half the intake of food. X-ray examination of the lungs on February third showed that the condensation in the right middle lobe had diminished since the examination in October; it appear as streaked and punctiform condensations. Moreover, elongated bronchial lumina were seen to extend down towards the diaphragm. Around both hili streaked condensations were in evidence, with increased perihilar configuration. In the left lower field, also some wide bronchial lumina were seen. Duodenal probing with aspiration of pancreatic juice after in-

jection of secretin was performed and 5 cc was aspired for analysis. This showed no trypsin. Culture of the duodenal juice showed growth of B. coli. The stools on admission were large, grayish and foul-smelling, about 140 g per day, with a dry matter content of 25 %. X-ray examination of the small intestine showed passage to be normal. There were no symptoms suggesting a coeliac syndrome.

After establishment of the diagnosis of congenital cystic fibrosis of the pancreas, with typical case history and clinical findings, including discontinued production of trypsin, the patient was put on a diet low in fats and rich in carbohydrates, with the protein content normal for children of the same age, vitamins A, B, C and D in large doses, and 80 000 units of penicillin daily, for 3 weeks.

Her condition, however, became aggravated; although the bouts of coughing remained unchanged, the vomiting increased and her weight decreased slowly, so that after having stayed 1 month in hospital she weighed 3 500 g. Since it was obvious that the feeding excited the bouts of coughing and these in turn gave rise to the large vomits, it was decided to attempt to ingest food dropwise through a permanent stomach tube. A very thin tube was passed down through the nose, and through this tube the diet prescribed was ingested dropwise continuously. Immediately the vomiting ceased entirely. During the first few days the same diet was given as previously, i.e. 1 000 ml per 24 hours, and in connection herewith the patient ran a temperature of up to 40° C. and had thin stools. These were considered due to an acute irritation of the intestine because of the sudden, unaccustomed overfilling with nourishment. The diet was, therefore, changed to consist only of skimmed human milk with 5 % glucose, 5 % glucose solution and common salt solution, and the next day the temperature was normal and the stools no longer thin. In the course of 24 hours the patient received a total of 700 ml of fluid, corresponding to about 170 ml per kilo per day; about 500 ml of this quantity was skimmed human milk with 5 % glucose. Thanks to this permanent tube-feeding, the child's weight rose by 570 g in the course of the

next 9 days, while the hemoglobin decreased correspondingly from 93 % to 65 %, the serum protein from 9.5 % to 6.5 %, the N. P. N. from 41 mg % to 34 mg %, and the hematocrit from 43 % to 34 %. On account of low serum chloride values (57 mmol. as opposed to the normal 75 to 100 mmol.), additional administration of in all 21 g NaCl in the course of 1 week was prescribed. This made the serum chloride rise to 81 mmol. As the serum protein declined and as after having been fed by tube for 1 week the patient developed edemas of the dorsum of the hands and eyelids, a blood transfusion was given intratibially, 80 ml of citrated blood from the patient's father. In connection with this a severe cough set in and the patient brought up large amounts of thick yellow pus. She grew increasingly dyspneic, with a rising temperature which on the following morning was 41° C, and clear signs of bilateral pneumonia. The condition rapidly became aggravated and death followed in the evening.

Autopsy showed the surface of the pancreas to be irregular. It was of firm consistency but without visible cystic formations. The weight was 10 g. The lungs showed diffuse distended bronchi with copious, viscid, yellowish-white contents, in places with bronchopneumonias. Nowhere were there any signs of irritation caused by the tube.

Microscopic examination revealed typical cystic pancreatic fibrosis with striking inflammatory cellular infiltration. Microscopic examination of the lungs showed bronchiectatic changes with bronchitis and peribronchitis.

As the vomiting ceased upon institution of permanent feeding by stomach tube, the possibility was presented of making a study of the patient's fat resorption. This was completed within 72 hours, during which period the stools were identified by means of carmine and collected quantitatively, while at the same time a careful check was made on the intake of food. The latter, as has been mentioned, consisted of skimmed human milk (pasteurized) with 5 % glucose and common salt solution. A total of 1 540 ml of skimmed human milk was given during the experimental period and the patient excreted 102 g of feces. 10 ml of the milk was pipetted off daily; these samples were pooled

and sent away for a fat analysis, which gave the following result: 1.98 % total fat, consisting of 8 % free fatty acids, 44 % neutral fat, and 48 % linked fatty acids. Fat analysis carried out on wet feces gave 13.4 % total fat consisting of 51 % free fatty acids, 25 % neutral fat and 24 % linked fatty acids.

During the experimental period a total amount of 1 540 ml skimmed human milk was thus administered, containing altogether 30.8 g of fat, 2.5 g of which were free fatty acids and 28.3 g of which had not undergone hydrolysis. With the 102 g of feces 13.7 g of fat was excreted in all, 6.7 g being free fatty acids and 7 g unhydrolized fat.

Of the 30.8 g of fat a total of 13.7 g, or 44 %, was thus excreted.

In the experimental period 28.3—7 = about 21 g were available for hydrolization. Of this quantity 6.7—2.5 = about 4 g were excreted with the feces after digestion; this means that 21 — 4 = about 17 g of fat were resorbed in the course of 72 hours, giving a resorption of 5.7 g of fat per day. If the patient's capacity to digest and utilize the intake of human milk is now considered, the following result is obtained with an intake of 510 ml per 24 hours.

Of the milk fat 5.7 g is resorbed per day, representing a caloric value of 9	=	51 calories
Of the protein roughly 1/2, or 3 g, is estimated to have been resorbed	=	12 calories
Of the milk sugar the whole amount, 36 g, caloric value 4, was resorbed	=	144 calories
Of the 510 ml of skimmed human milk which has been ingested per day the patient utilized	=	207 calories.

Assuming the requirement to be 100 calories per kg per day the ingestion in the patient here concerned (weight 4 kg) would have to be 400 calories per day, of which it would be possible to ingest only about 200 calories per 500 g human milk. If the requirement were to be covered, it would be necessary to give either 1 000 ml of human milk, corresponding to 250 ml of fluid

per kg per day, or make up the deficiency of 200 calories by adding 50 g of glucose per day. The patient received a daily addition of only about 30 g of glucose, and thus there was a deficiency per day of not less than 80 calories. Instead of a 5 % glucose supplement to the human milk, at least 10 % should have been added. If in the calculation of calories the ideal weight of the patient for the age (6 months, corresponding to about 6 kg) is taken as a starting point, the requirement per day is found to be 600 calories and the caloric deficiency thus considerably higher.

I have succeeded in tracing only 3 cases in the literature (reported by Dorothy Andersen (1)) on fat resorption in children with congenital fibrosis of the pancreas relating to children under 6 months. The values from Dorothy Andersen's normal material (2) as well as from her 3 cases of congenital pancreatic fibrosis and from the case here reported are shown in the table.

	From Dorothy Andersen (1) and (2)				Own Case
	Average of 11 Normal Children	3 children With Congenital Pancreatic Fibrosis			
Age in Months	2—6	$1\frac{1}{2}$	$2\frac{1}{2}$	4	6
Daily Intake of Fat in g	»normal diet»	17.5	18.3	13.7	10.3
Feces, Wet Weight, g/Day	6.6 —37	23.5	17.5	13.2	34
Total fecal Fat, g/Day	0.29— 1.30	4.2	3.3	2.4	4.6
Neutral Fat % of Total Fat	7.8 —51.9	27	31	22	51

The analyses from Dorothy Andersen's 3 cases are not directly comparable with mine because there is such a great difference in the daily intake of fat. On comparison with the normal figures it will be seen that the amount of feces, 34 g, excreted daily by my patient was within the limits of the normal, whereas the amount of fat excreted was considerably above normal (4.6 g as against 1.30 as the highest normal value). Furthermore, it will be seen that in my case the percentage of neutral fat was very near the upper limits of the normal, 51 %, while the highest normal value is 51.9 %. Unfortunately the possibility of bac-

terial hydrolysation of the neutral fat to free fatty acids after defecation — as demonstrated by Dorothy Andersen 2) — escaped our attention, for which reason the fecal samples were not placed in a refrigerator. Possibly this omission is responsible for the fact that the values found for the percentage of neutral fat are not definitely increased, as was to be expected in a case of such definitely reduced pancreatic function, since it is precisely the increase in the neutral fat fraction in the feces which is typical of pancreatic insufficiency 2), although it need not be present 2).

Thus it is evident that in the case of severe congenital cystic pancreatic fibrosis reported the reduced pancreatic function was responsible for 1) a undernourishment of the patient, 2) a daily excretion of fat which despite a diet low in fat was about 4 times the fat excretion in normal children of the same age on a diet with a normal content of fat, and 3) possibly an increase in the neutral fat in the feces.

It should be emphasized that in cases of this kind attention should be directed more than has hitherto been customary to the purely quantitative aspect of the intake and utilization of calories, if necessary based on analyses of the fat resorption as here described.

Summary

The author reports the case history and clinical and laboratory findings for a patient aged 6 months with congenital cystic fibrosis of the pancreas, the diagnosis of which was made clinically and verified at autopsy. A considerable increase in the weight of the extremely emaciated child was achieved by ingesting food through a permanent stomach tube.

Experiments on the fat balance showed that in an experimental period of 72 hours during which the patient received a total of 30.8 g of fat, 13.7 g (= 44 % of the intake) was excreted. It is demonstrated that because of the reduced pancreatic function the patient became undernourished, the deficiency being at least 80 calories per day on the diet employed. Compared with the values from a normal material published by Dorothy Andersen,

it is seen that the patient's daily excretion of fat was 4 times the normal, while the weight of the feces and the percentage of neutral fat contained in them were within normal limits, although very near the upper limit.

Résumé

L'auteur relate l'histoire de la maladie ainsi que des découvertes cliniques et de laboratoire, chez un patient de 6 mois atteint d'une fibrose kystique congénitale du pancréas, dont le diagnostic avait été fait en clinique et vérifié à l'autopsie. Une forte augmentation de poids de l'enfant extrèmement amaigri, fut obtenue en le nourrisant au moyen d'un tube d'estomac à demeure. Lors de la vérification le bilan du métabolisme des graisses, on a constaté, qu'en une période d'expérience de 72 heures, pendant laquelle le patient a reçu un total de 30.8 g de matières grasse, 13.7 g (= 44 % de cette quantité) furent excrétés. Il est démonstré que, par suite de la réduction de la fonction de son pancréas, le patient était sousalimenté; le déficit s'élevait à au moins 80 calories par jour du régime employé. Comparé avec les chiffres d'un matériel d'étude normal publié par Dorothy Andersen, on a constaté que l'excrétion de graisse quotidienne du patient était 4 fois la normale tandis que le poids des fèces et le pourcentage de graisse neutre qu'elles contenaient était dans les limites normales quoi que très près du maximum.

Zusammenfassung

Der Autor berichtet über die Krankengeschichte sowie die klinischen und Laboratoriumsbefunde bei einem 6 Monate alten Patienten mit kongenitaler cystischer Pankreasfibrose, welche klinisch diagnostiziert und durch die Autopsie bestätigt wurde.

Durch Nahrungszufuhr mittels permanenter Magensonde wurde bei dem extrem abgemagerten Kinde eine bedeutende Gewichtszunahme erreicht. Untersuchungen über die Fettbalance zeigten, dass in einer Versuchsperiode von 72 Stunden, während welcher der Patient eine Gesamtmenge von 30.8 g Fett erhielt, 13.7 g (44 % der zugeführten Menge) ausgeschieden wur-

den. Infolge der herabgesetzten Pankreasfunktion kam es zu Unterernährung des Patienten, das Defizit betrug mindestens 80 Kalorien täglich bei der angewendeten Diät. Verglichen mit den von Dorothee Andersen veröffentlichten Werten eines Normalmaterials zeigt sich, dass die tägliche Fettausscheidung des Patienten das 4fache des Normalen betrug, während das Gewicht der Fäces und ihr prozentueller Gehalt an Neutralfett innerhalb normaler Grenzen, wenn auch sehr nahe der oberen Grenze, lag.

Resumen

El autor informa sobre la historia y los hallazgos clínicos y de laboratorio de un enfermo de 6 meses con cística fibrosis congénita del páncreas; el diagnóstico se hizo clínicamente y se verificó por medio de autopsia. Un considerable aumento del peso del niño sumamente enflaquecido se efectuó ingiriendo comestibles por un tubo permanente del estómago. Los experimentos relativos al balance de grasa demostraron que durante un período de ensayo de 72 horas, durante cuyo período el enfermo recibió en total 30.8 gramos de grasa, se excretaron 13.7 gramos (: 44 % de la ingestión). Se ha demostrado que a causa de la función reducida del páncreas el enfermo resultó desnutrido. La deficiencia fué por lo menos de 80 calorías por día con la dieta empleada. Comparado con los valores de un material normal publicado por Dorothy Andersen, se nota que la excreción diaria de grasa del enfermo era 4 veces la normal, mientras que el peso de los heces y el porcentaje de grasa natural contenida en los mismos estaba dentro de los límites normales, aunque muy próximo al límite superior.

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FROM BORÅS HOSPITAL, PEDIATRIC DEPT. (HEAD: B. SÖDERLING, M. D.)

The Significance of Chvostek's Symptom in Infants under Two Years of Age

by

KJELL L. MÖLLER and BERTIL SÖDERLING

According to most manuals and textbooks on diseases of infancy and childhood, the distinct presence of the facial phenomenon or Chvostek's sign is still considered pathognomonic or at any rate highly suggestive of spasmophilia or infantile tetany (GRAHAM, GUILD, IBRAHIM, MOURIQUAND). This opinion seems to be shared by most pediatricians. A number of cases which constitute exceptions to this medical rule have been reported, however, i. e. cases in which an abnormal sensitiveness of the nerves to mechanical stimulation was present in children under 2 years of age without any apparent co-existent spasmophilia (KLEINSCHMIDT, LUST, WERNSTEDT). Furthermore, it has been generally accepted that positive facial phenomena of non-spasmophilic nature may be elicited in newborn and older children. WERNSTEDT states that spasmophilia can be diagnosed only on the basis of a combination of several symptoms, and not simply on the presence of this facial reaction due to hypersensitiveness.

In Sweden NAGLO studied Chvostek's sign in a material consisting of some 5 000 inmates and out-patients of a children's hospital and polyclinic (Wernstedt's Clinic). He found a positive reaction in 19.9 per cent of the 2—3 year-old children, in 14.6 per cent of the 3—4 year-old group, and in 32.6 per cent of the 8—13 year-old group. A number of male adults were also tested and showed an incidence of 2—3 per cent. In children 0—2 years old Chvostek's symptom could be induced in 9.6

per cent, or 154 cases. The vast majority of these 154 cases were nearly 2 years old. In 20 of these infants spasmophilia could be excluded, as was also the case in a small group of 3 children under 2 months of age. The other 131 cases were considered spasmophilic. According to NAGLO, in spasmophilia the facial phenomenon is more pronounced in the upper branch of the facial nerve or equal in both branches, while in the absence of this disorder the reaction is stronger in the lower branch. NAGLO draws the conclusion that the presence of Chvostek's symptom is not absolutely pathognomonic of spasmophilia in infants under 2 years of age.

At Borås, as also elsewhere in Sweden, we have the definite impression that nowadays spasmophilia so seldom occurs that it may be considered a rarity. In the course of the last 5 years we have neither treated nor heard of a single case of manifest spasmophilia at our Children's Welfare Centres. During this period 8 cases of spasmophilia have been admitted to the Children's Department of the Hospital of Borås. Although this figure cannot, of course, be used as a basis for a statistical calculation of the incidence of the disease, it certainly does most distinctly indicate the strikingly low frequency of infantile tetany nowadays as compared with what it used to be.

Nevertheless, children under 2 years of age with an elicitable facial phenomenon are not infrequently observed at our Children's Welfare Centres. If the presence of this sign alone were indicative of spasmophilia, the disorder would not be uncommon. This seems to be in disagreement with the above-mentioned experience of the frequency of manifest spasmophilia. During the years 1942—1946 43 cases were therefore selected for special observation. *The cases chosen consisted of children up to 2 years of age who were well cared for, who were prophylactically treated with an ample administration of D-vitamin, who were brought up mainly on mother's milk, and in whom the facial phenomenon was distinctly elicitable.* When the phenomenon was first observed in each case during a visit to the Children's Welfare Centres, these visits taking place at relatively different times of the year, the average age of the children was 14.4 months. 18 of the cases

consisted of babies 7—12 months of age. None of the cases selected showed any distinct signs of rickets. In some cases the reaction was so easy to elicit that even slight finger percussion sufficed to evoke very noticeable twitching. In many cases the D-vitamin treatment was initiated with 2 heavy doses (Fortedol) of 500 000 I.U. with an interval of 2 weeks. Every child was tested regularly for the facial symptom at every visit until released from the Centre. *In 2 cases only did the facialis phenomenon disappear in the course of the observation time, which lasted on an average 7 months before the children were discharged.* A further examination was made in the spring and autumn of 1948. Even on this occasion, on an-average *4 1/2 years after the first detection* of the facial phenomenon, it was still possible to elicit *the sign distinctly* in all the *observed cases* except 2, i. e. in 32 children.

Further evidence is superfluous. It was our opinion from the very beginning that these well cared for children prophylactically treated with D-vitamin and without other manifest symptoms suggestive of spasmophilia could hardly be suffering from this disorder. In 12 cases the serum calcium was determined upon discovery of the facial phenomenon and the skeleton was roentgenologically examined, but without any pathologic findings. Conclusive evidence that the facial phenomenon was not ascribable to spasmophilia in these children under 2 years of age was provided by the follow-up examinations.

It should further be noted that the children selected were not neuropathic; it is our opinion that the facial phenomenon in the present cases was just as little ascribale to any type of neuropathy as to spasmophilia. Neither were the children of uniform constitutional type. It may be wisest not to indulge in any speculations but to leave the question of pathogenesis open. We should like with this short contribution merely to point out *that the insignificant facial phenomenon present in older children may to a certain extent be elicited in the same children even in babyhoos, when it is probably of the same innocent nature.* Thus even in babyhood the facial phenomenon is of very limited value in the diagnosis of spasmophilia.

Summary

The positive facial phenomenon or Chvostek's symptom is not infrequently demonstrable in infants and children under 2 years of age without any co-existent symptoms suggestive of infantile tetany. The phenomenon may be elicited in unchanged form for many years. It thus seems as if its presence in the spasmophilic age may be of the same innocent nature as it is in older children. Neither does it seem to be pathognomonic of neuropathy.

Résumé

Il n'est pas rare que l'on puisse constater le signe facial, ou symptôme Chvostek, chez des nourrissons ou des enfants audessous de 2 ans, sans la coexistence de symptômes causés par la tétanie infantile. Le signe peut subsister de nombreuses années sous sa forme primitive, inchangée. Il semble donc que sa présence à l'âge de la spasmophilie puisse être de la même nature anodine que chez les enfants plus âgés. Il ne semble pas non plus être pathognomonique de la neuropathie.

Zusammenfassung

Das positive Facialisphänomen oder Chvosteks Symptom kann relativ oft bei Säuglingen und Kindern unter 2 Jahren nachgewiesen werden ohne dass gleichzeitig Symptome infantiler Tetanie vorhanden sind. Das Phänomen kann in unveränderter Form jahrelang bestehen bleiben. Es scheint also das Vorhandensein desselben im Spasmophilie—Alter derselben harmlosen Natur zu sein wie bei älteren Kindern. Auch scheint es nicht pathognomonisch zu sein für eine Neuropathie.

Resumen

El fenómeno positivo, facial, del síntoma de Chvostek se puede muchas veces observar en criaturas y niños de menos de 2 años de edad, sin ningún otro síntoma coexistente, sugestivo de tetania infantil. El fenómeno se puede educir en forma inalterada durante muchos años. Parece, por consiguiente, que su pre-

sencia durante la edad espasmofílica es de la misma naturaleza inofensiva que en niños de mayor edad. Tampoco parece ser patognomónico de neuropatía.

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On Parahemophilia, a Hitherto Unknown Hemorrhagic Disease

by

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Hemophilia is »an hereditary disease affecting males, transmitted by females and characterized by a prolonged coagulation time and a life-long tendency to excessive hemorrhage» (WHITBY and BRITTON (1)). »Hemophilia is a hemorrhagic disease of constitutional origin, usually familial, limited to the male, but transmitted by the female. It is characterized by a delay of coagulation of the blood and associated with a tendency to bleed, especially after trauma» (DIAMOND (2)). Hemophilia is so striking and spectacular in its symptomatology that it is one of the diseases which has been known for at least two thousand years. The statement of BULLOCH and FILDES (3) that the earliest description of hemophilia in literature is of as early date as the year 1519 is incorrect. In that year the Latin translations of the papers of the Arab physician ABULKASIM—EL—ZAHREWI (4) were published. As he died in Cordova, Spain, in 1106 or 1107, there is no doubt that the cases described by him in the 11th century are the first reports on hemophilia in medical literature. PREUSS (5) in his monograph »Biblisch-talmudische Medizin» stressed the fact that according to Rabbi SIMON BEN GAMALIEL, if a mother lost two male offsprings owing to ritual circumcision (on the eighth day after birth), further sons might be exempted from circumcision. This indicates that the disease has been known for almost two thousand years. No wonder that there are excellent descriptions of it by HOECHSTETTER (6) in the

17th century and FORDICE (7) in the 18th century. The fact that in 1803 OTTO (8) described the heredity pattern of hemophilia and that NASSE (9) was able to furnish evidence of the peculiar-sex linked heredity on a large material in 1820 are well known. GRANDIDIER (10), in Germany, published an excellent monograph, 158 pages long, on hemophilia in 1855; the second edition, issued in 1877, was already 227 pages long. He reported 657 cases of hemophilia in the second edition. In 1922 K. H. BAUER (11) reported on 653 family trees with hemophilia. Thus hemophilia has not been considered a rare disease. It is spread all over the world. While it seems that it is more frequent among Caucasians, CRANDALL (12) and PACHMANN (13) reported cases among Negroes, FUJI (14) in 1933 61 instances in Japan, and TUPAS, DAUIS, and CABIGTING—CHAVEZ (15) cases among Filipinos.

While the symptomatology of hemophilia is well known, there are different opinions as to the etiology. All agree however, that hemophilia is characterized by prolonged coagulation time; the clotting time may vary, but it is never normal. On the average it is around 2 hours, sometimes even 7 to 12 hours. Thus a constantly prolonged clotting time is an inherent factor in the etiology of the disease and stressed in the definitions of it. However, according to FONIO (16) the bleeding tendency in hemophilia may not be due exclusively to delayed coagulation. He claims that in some cases so much fibrinolysis may be observed in vitro that parts of the blood already coagulated may again be liquefied. If this is true, there is a possibility that hemorrhagic disease similar to hemophilia may develop even without delayed clotting of the blood. It may be, however, that other unknown factors in the coagulation mechanism may bring about hemorrhagic diseases which do not tally with our ideas about hemophilia. It is futile to discuss here the possible etiology of the prolonged coagulation time. While the majority of researchers (HOWELL (17), FONIO (16) *and others*) claim that the delay is due to lack of thromboplastin in the platelets, TOCANTINS (18) believes that the main factor is antithromboplastic activity in the blood plasma of hemophiliacs.

VAN CREFELD (19) believes that the delayed coagulation is due to a plasma factor and not to the platelets. PATEK and STETSON (20) claim in their turn that a clot-promoting factor is absorbed by the platelets in the blood of hemophiliacs, while LOZNER and *co-workers* (21) and TAYLOR and *co-workers* (22) attribute the delayed clotting to the lack of a globulin fraction. At any rate, the different theories concerning the possible etiology of the delayed coagulation time suggest that there may be other hemophilia-like diseases in which the coagulation time is not affected.

Recently we observed a family the symptomatology of whose disease definitely suggested hemophilia. The bleeding tendency had been familial, congenital, affecting only male members of the family, and the bleeding had been definitely traumatic and not spontaneous. But the coagulation time was always normal. We could rule out, to be discussed later, all other known forms of hemorrhagic diseases. As the symptoms had been hemophilia-like, while the clotting time was normal, we labelled the cases as »parahemophilia», a hemophilia-like disease, but probably different in etiology and different in the cause of bleeding.

Carlos, S. D., a two year old Filipino male child, was admitted on October 14, 1948, on account of uncontrollable bleeding from a wound in the occipital region. On the day before admission, the child had bumped his skull against the edge of a closet. Bleeding was profuse. A physician sutured the wound with two stitches; the bleeding stopped for half an hour and then started again. One half year before admission a small wound on the right thumb had bled profusely for one week. For one year the child had been suffering from repeated ecchymoses all over the body.

Upon admission the child was strikingly pale. There was continuous produse bleeding from the sutured wound. The child was well nourished and well developed; on objective findings there were besides the bleeding some ecchymotic patches at the right buttock and popliteal area, and a small hematoma in the right malleolar region. The blood findings were as follows:

Hemoglobin	3.5 gm. per 100 cc. blood
Red cell count	2,470,000 per cmm. blood
White cell count	7,400 per cmm. blood
Platelet count	420,000 per cmm. blood

Volume-packed red cells	17.0 per cent
Mean corpuscular volume	68.8 cu. mi.
Mean corpuscular hemoglobin	14.1 mi. mi.
Mean corpuscular hemoglobin concentration	20.5 per cent
Volume Index	0.79
Color Index	0.49
Saturation Index	0.60
Clotting time	5 minutes (venous blood)
Bleeding time	35 seconds
Prothrombin time	31 seconds
Retractility of the clot	completely normal
Tourniquet test	negative
Capillaries of the nail	normal, no tortuosities

Differential count:	B	E	M	J	St	S	L	Mo
	—	2.4	—	—	4.0	53.6	32.8	7.2

marked anisocytosis, poikilocytosis, polychromatophilia, microcytosis, hypochromia; no nucleated red cells-Post hemorrhagic acute anemia-Stool examination: ascaris ova ÷ no other pathological findings.

At first, topical thrombin was applied on the bleeding wound. The bleeding did not stop, however, and therefore blood transfusion (190 cc.) was administered on the day of admission. As the bleeding did not stop, 250 cc. blood was administered again the next day. After the second transfusion there was some slight oozing of blood, but the hemorrhage was stopped completely. Two more blood examinations were made afterwards. On October 22, the hemoglobin level was 4.2 gm. per cent; on November 1, 7.4 gm. On October 22, there were 4 nucleated red cells to 250 white cells, on November 1, no nucleated red cells anymore. The child went home much improved and free of hemorrhagic symptoms on November 1.

As TUPAS, DAUIS, and CABIGTING—CHAVEZ (15) described the two cases which occured in the same family and published the family tree of these cases, we shall here take advantage of their report. The oldest brother of our case was observed in the Philippine General Hospital in 1945. At that time he was suffering from bleeding from the gums owing to a ruptured swelling of a periostitis of a molar. He suffered, like his younger brother, from profuse hemorrhage following the rupture of an occipital boil. Between the ages of four and seven he also suffered from traumatic bleedings and from time to time had recurrent ecchymotic bleedings as well. There had been hemorrhages in the right

knee and elbow joint, at which time a clotting time of 16 minutes and 45 seconds for venous blood was reported along with normal platelet count with normal bleeding time and normal retractility of the clot. We examined the blood of this boy again during the stay of his younger brother and found:

Hemoglobin	11.15 gm. per 100 cc. blood
Red cell count	4,430,000 per cmm. blood
White cell count	4,400 per cmm. blood
Volume packed red cells	31.0 per cent
Mean corpuscular volume	70.0 cu. mi.
Mean corpuscular hemoglobin	22.4 mi. mi.
Mean corpuscular hemoglobin concentration	32.0 per cent
Volume Index	0.80
Color Index	0.78
Saturation Index	0.94

Differential count:	B	E	M	J	St	S	L	Mo
	—	15.2	—	—	3.2	48.0	27.2	6.4

no signs of anemia. The eosinophilia was due to ascariasis

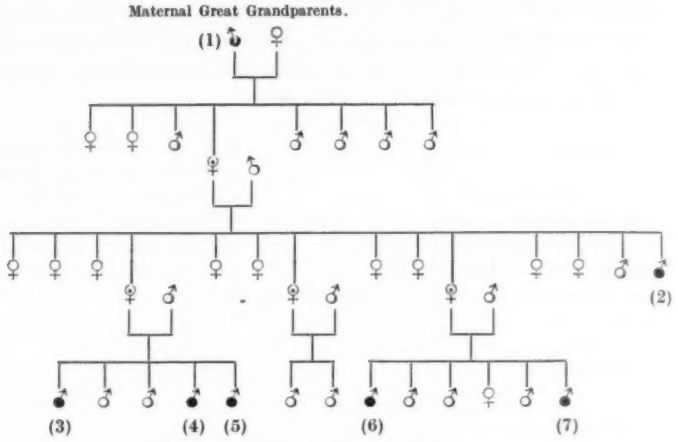
Coagulation time (venous blood)	7 minutes
Retractility of the clot	normal

Thus it may be stressed that even in this brother with history and symptoms strongly suggesting hemophilia, the coagulation time turned out to be normal.

The first cousin of the two boys was admitted according to TUPAS, DAUIS, and CABIGTING—CHAVEZ (15) in 1946 with hemarthrosis, ecchymoses and a history of traumatic bleedings. There had been no anemia; platelet count normal, clotting time 7′30″ (venus blood), bleeding time 1′30″, retractility of the clot normal, tourniquet test negative. The family tree drawn by the same authors and including our own observations was as follows. (See the family tree on the next page.)

From this family tree the heredity, which is completely analogous to that of hemophilia, can be clearly appreciated. This heredity pattern rules out immediately, even without consideration of other hematologic symptoms, thrombasthenia and hereditary thrombopathy. According to WHITBY and BRITTON (1)

Family Tree of Cases



(4) is our patient; (3) and (5) his brothers; (6) and (3), cases described by TUPAS and associates, and; (2) an uncle who died due to hemorrhages.

(♂ sick male; ♂ healthy male; ♀ carrier females; ♀ apparently healthy females).

Table I. Diffential Diagnosis

	Heredity	Sex	Clotting Time	Bleeding Time
1. Hemophilia	yes	males	much prolonged	normal
2. Parahemophilia	»	» ?	normal	»
3. Willebrand's Syndrome	»	both sexes	»	prolonged
4. Hereditary Thrombasthenia	»	» »	»	» ?
5. Thrombopenic Purpura	no	» »	»	»
6. Vascular Purpura	»	» »	»	normal
7. Hereditary Hemorrhagic Teleangiectasis	yes	» »	»	»
8. Afibrinogenia Congenita	»	» »	absent	»
Acquired Fibrinopenia	no		very prolonged	

hereditary thrombasthenia (GLANZMANN (23)) is »an hereditary disease appearing in males and females characterized by purpura and bleeding, a prolonged bleeding time, a failure of clot retraction, a normal coagulation time and with usually slight or no reduction of the platelets». As to hereditary thrombopathy (von WILLEBRAND's disease (24)), their definition is: an hereditary disease appearing in males and females, characterized by a tendency to bleed, a prolonged bleeding time, a normal coagulation time, efficient clot retraction and with no reduction of platelets. »It is obvious that our observations do not fit either of the two diseases. In order to give a better survey of differential diagnosis between the different hemorrhagic diseses, we shall at this point summarize in a table the symptomatology of the different hemorrhagic diseases with the exception of the hemorrhages due to prothrombinopenia.

GEIGER and EVANS (25) collected the cases labelled as von WILLEBRAND's syndrome in the literature up to 1938. There were 43 male and 54 female bleeders out of 125 males and 128 females in the bleeder families. Therefore it is obvious that this

of Hemorrhagic Diseases

Retractility of Clot	Platelet Count	Fibrinogen	Prothrombin	Capillary Fragility	Purpuric Spots	Ecchymoses
normal	normal	normal	normal	normal	absent	present
»	»	»	»	»	»	»
»	»	»	»	increased	»	»
poor	»	»	»	normal or increased	present	may be present
very poor	decreased	»	»	increased	»	may be present
normal	normal	»	»	normal or increased	»	mostly absent
»	»	»	»	normal	absent	»
—	»	absent decreased	»	»	»	present

kind of hemorrhagic disease is not sex linked. The same authors likewise tabulate cases of hemorrhagic diseases according to their resemblance to hemophilia and thrombocytopenic purpura. We quote their tabulation with the addition of our cases of »parahemophilia»:

Table II.

Differential Diagnosis of Diseases Between Hemophilia and Purpura

Syndromes	Heredofamilial	Manifested in Both Sexes	Prolonged Bleeding Time	Prolonged Clotting Time	Thrombocytopenic	Local capillary Resistance	Poor Retractility of the Clot	Hemophilia Resemblance	Purpura Resemblance
Hemophilia	+	—	—	+	—	—	—	—	—
Parahemophilia	+	—	—	—	—	—	—	6	1
HANDLEY and NUSSBRECHER (26)	+	+	—	+	—			4	1
VAN DER ZANDE (1 case) (27)	+	+	—	+	—		+	4	2
BUCKMAN (28)	+	+	+	+	—		—	4	2
CURSHCHMANN (28)	+	+	+	—	—	—		3	3
GLANZMANN (8 families) (23)	+	+	—	—	—		—	3	3
KROEMEKE (5 cases) (30)	+	+	—	—	—	+		3	3
VAN DER ZANDE (1 case) (27)	+	+	—	—	—		—	3	3
ROTHMAN and NIXON (31)	+	+	+	—	—	+	—	3	4
VON WILLEBRAND (24), MINOT (32), GIFFIN (33), ROSLING (34), LITTLE and AYRE (35), GEIGER and EVANS	+	+	+	—	—	+	—	3	4
GLANZMANN (1 family) (23)	+	+	+	—	+		+	2	4
KROEMEKE (1 case) (30)	+	+	+	—	+	+	+	2	5
HESS (36)	+	+	+	—	+	+		1	5
Thrombocytopenic Purpura	—	+	+	—	+	+	+		

This tabulation provides evidence that there are plenty of ill-defined hemorrhagic diseases between hemophilia and thrombocytopenic purpura, at least symptomatically, and we are still far from having a definite, satisfying classification of hemor-

rhagic diseases. At the same time we see, that there is not a single syndrome among fourteen different syndromes so near to hemophilia as parahemophilia. It is hard to restrain ourselves from discussing the different possibilities which might bring about the different syndromes. But our purpose is to call the attention to the *type* of hemorrhagic disease presented here. We are aware that a few cases are not yet sufficient to furnish final evidence of a disease not described hitherto. However, the familiarity and heredity are so striking that we considered it worthwhile to publish our experiences so far. We hope to have more cases in the next future in order to be able to observe further details of this interesting disease. We consider this paper a preliminary publication which may be followed by more detailed observations.

Summary and Conclusions

Three cases of a hemorrhagic disease with all the clinical symptoms of hemophilia but normal coagulation time are described in the same family. The family tree likewise suggests hemophilia. As hemophilia is characterized by a constantly prolonged clotting time, however, we label our cases »parahemophilia» for the time being. Symptomatology and differential diagnosis of the disease are discussed.

Résumé

Description de 3 cas de maladie hémorragique avec tous les symptômes cliniques d'hémophilie, mais un temps de coagulation normal, dans une même famille. Le tableau généalogique de la famille indique aussi l'hémophilie. Cependant, comme l'hémophilie se caractérise par un temps de saignement prolongé constant, nous désignons actuellement nos cas du nom de »parahémophilie». La symptômatologie et le diagnose différentiel de cette maladie sont discutés.

Zusammenfassung

Es werden 3 Fälle einer Blutkrankheit mit allen Klinischen Symptomen der Hämophilie, jedoch mit normaler Coagulations-

zeit bei derselben Familie beschrieben. Der Stammbaum spricht gleichfalls für Hämophilie. Da die Hämophilie durch eine konstant verlängerte Gerinnungszeit charakterisiert ist, bezeichnen wir unsere Fälle vorläufig als »Parahämophilie». Symptomatologie und Differentialdiagnose der Krankheit werden erörtert.

Resumen

Se describen tres casos, todos en una misma familia, de una enfermedad hemorrágica con todos los síntomas clínicos de la hemofilia, pero con tiempo normal de coagulación. Parece que en los antepasados ha habido también casos de hemofilia. En vista de que la hemofilia se caracteriza por la constante prolongación del tiempo de coagulación, se ha designado a estos casos con el nombre de »parahemofilia». Se discute la sintomatología y la diagnosis diferencial de la enfermedad.

Additional Note

Since our paper was finished, HALLIWELL and BRIGHAM's paper on Pseudohemophilia, Annals of Internal Medicine 29: 803, 1948 (November) has been issued. The authors report on five males in one family aged 77, 27, 2—8, 7—29 and 6 years during the observation period. In all instances the coagulation time, platelet count, retractility of the clot, prothrombin time and capillary fragility were normal, while the bleeding time was prolonged in four instances, although in one it was normal. There was no case among the female members of the family. The authors quoted the pater of ESTREN, SANCHEZ—MEDAL and DAMESHEK on Pseudohemophilia (Blood 1: 504, 1946), which, not being available in the original in our warravaged libraries, could not be quoted by us. A further reason for omission of this paper is that its authors claimed that their pseudohemophilia was observed in both sexes and that beyond prolonged bleeding time, there were no abnormal findings in the blood. It may be admitted, however, that the cases of HALLIWELL and BRIGHAM are very similar to ours, as the symptomatology is similiar, the

disease is restricted to the male sex, and the prolongation of the bleeding time is not very marked.

We did not discuss the question of possible anticoagulants in the blood as the coagulation time has been normal in our cases, and we wonder if anticoagulants can be inherited.

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Foreign Bodies in the Esophagus with Symptoms Exclusively from the Air Passages

by

H. FR. FABRITIUS

Foreign bodies in the esophagus in children is no rarity. The symptoms are usually characteristic and will seldom give rise to diagnostic difficulties. However, the usual clinical signs may occasionally be missing, and noncharacteristic symptoms may lead one astray so that the presence of a foreign body is overlooked. Perhaps C. P. SCHENK's (1) view expressed in an article on foreign bodies, that: »in the case of a sick child the possibility of a foreign body in the food or air passages should always be considered,» is not too ex-parte.

The typical symptoms of a foreign body in the esophagus are dysphagia or aphagia, odynophagia, vomiting, dyspnea, and cough (the latter as a result of reflex irritation), secretion floating over to the larynx, or a fistula of the trachea. As a rule several of the symptoms will be present and most physicians are aware of the fact that foreign bodies in the esophagus may produce symptoms from the air passages *also*, especially if the foreign body is large or has produced a reactive swelling after having remained for a while. In the following text the cases of 2 children are reported, which show that large foreign bodies may lodge in the esophagus for a considerable period of time without interference to swallowing and with symptoms from the air passages as a predominant feature.

The first patient is a $1\ ^1/_2$ year old girl whose parents in May 1947 conceived a suspicion that she might have swallowed a button. She was admitted to a hospital and remained there a week,

but as nothing wrong was found either on clinical or roentgenographic examination, she was discharged. Some days later the child became febrile and was readmitted to the hospital, where she stayed for 14 days, but still with negative findings. Symptoms subsequently developed from the respiratory tract, however, and the local physician thought the child had bronchitis. She was dyspneic, with râles in the chest. Bronchopneumonia developed and soon healed, but respiratory distress and the râles persisted, although to a varying extent, and the condition had much of an asthmatoid character. During this period the child vomited on a few occasions, but there were no difficulties in swallowing. Finally a foreign body in the air passages was considered and an otolaryngist was consulted. A bronchoscopy was allegedly performed, but nothing abnormal was found and by the end of July the child was referred to the Ear, Nose, and Throat Department of the University Clinic in Oslo. On admission the child appeared somewhat exhausted and pale. She was afebrile. Her respiration was stridulous and markedly oppressed with something of an asthmatoid character, and bronchitic râles were heard over both lungs. Swallowing was not impaired. The roentgenologist's report read: »Slight compression of the trachea, possibly result of an enlarged thymus. No evidence of foreign body.» Ephedrine was administered, but was ineffective. *Bronchoscopy*, like the roentgenographic examination, revealed a constriction of the upper part of the trachea with a definite anterioposterior compression, but no other pathological changes. *Esophagoscopy* was then performed in an attempt to find an explanation of the tracheal compression. A large button — 23 mm in diameter — was found lying lengthwise in the upper part of the esophagus, where it was rather firmly embedded in granulations on both sides. This button had been lodged in the esophagus for $2\ ^1/_2$ months.

The next patient is a $1\ ^1/_2$ year old boy. He developed dyspnea in the beginning of July 1937. His condition varied, and at times his respiration was stridulous. The respiratory distress developed particularly in connection with meals. He vomited occasionally but difficulties in swallowing were not noticed. Roentgenographic examination of the chest and esophagus revealed nothing

abnormal. The examination was allegedly not quite successful, however the boy was attended by the local physician, who thought that the respiratory distress might indicate an allergic condition. During this period the boy had an attack of bronchopneumonia. As his condition remained unchanged, he was referred to the Ear, Nose, and Throat Department of the University Clinic in Oslo, a foreign body in the air passages being suspected.

At this point there was no impairment of the patient's general condition and apparently no distress despite some stridor. No adventitious sounds were heard over the lungs. The roentgenologist's report read: »Definite constriction of the trachea as seen in hyperplasia of the thymus; otherwise nothing abnormal, no evidence of foreign body.» In this patient *esophagoscopy* was performed right away and a button of the same size as in the previous case found in the upper part of the esophagus, in the same position. In this case also the button was rather firmly embedded in granulations on both sides. It had remained undetected for about 3 months.

In both patients a check-up examination a week after the removal of the foreign body showed that the esophageal wall had healed nicely, without evidence of stenosis.

In both patients symptoms from the respiratory tract predominated while symptoms from the digestive tract were negligible, as a result of which the foreign body remaining undetected for a rather long period, in the first case even despite the suspicion that the child might have swallowed a foreign body.

Symptoms from the respiratory tract seldom predominate as much as in the cases reported in this paper, however. In 1942, VAN DER MEULEN (2) reported the case of a 5 year old child in whose esophagus the foreign body — a ring — lodged for 2 years before being detected, despite repeated examinations, while the diagnosis and picture of the disease varied between asthma, bronchitis, and laryngitis. Otherwise the literature is limited mainly to textbook considerations, for which reason I have considered mention of these patients to be justified. In both cases the respiration had at intervals a certain asthmatoid wheezing character. In this connection I should like to call attention to

an observation of JACKSON & JACKSON (3) dealing with the symptoms from the respiratory tract caused by foreign bodies: »We have come to regard the asthmatoid wheeze as the most important sign of a foreign body, *and sometimes the foreign body is in esophagus.*»

Roentgenographic examination plays an essential part in revealing foreign bodies, and as several authors have emphasized (e. g., A. S. JOHNSTONE (4) and S. BROWN (5)) the patient should be x-rayed both with and without contrast medium. The lateral roentgenographic view of the neck shows 3 definite columns: anteriorly the trachea, posteriorly the cervical column, and between these the soft tissue, including the esophagus. BROWN (5) points out that in adults the ratio between the width of these 3 columns is normally very constant, but it is less constant in children. An increase in the width of the soft tissue shadow should always arouse suspicion that the cause may be a foreign body. In both cases the foreign bodies produced no shadow on the film because both buttons were made of wood. Consequently they would not be revealed on the roentgenogram without the use of contrast medium. But even in small children this procedure is seldom attended with much difficulty. The use of contrast medium is necessary because a large number of foreign bodies do not appear on the roentgenogram. SCHENCK (1), for instance, states that in a material including 137 foreign bodies, 47 per cent were inopaque.

Summary

The author reports on the cases of 2 children in whom large foreign bodies remained undetected in the esophagus for 2 $^1/_2$ and 3 months, respectively, despite repeated examinations. He points out that neither of the patients had noticeable difficulties in swallowing but that they presented almost exclusively symptoms from the respiratory tract. The symptoms were very confusing and thus involved diagnostic difficulties. The author discusses the two cases and among other things emphasizes the necessity of roentgenographic studies with contrast medium even for small children.

Résumé

L'auteur rapporte les cas de 2 enfants chez lesquels de gros corps étrangers sont restés inaperçus dans l'oesophages durant respectivement 2 $^1/_2$ et 3 mois malgré des examens réitérés. Aucun des patients n'avait de notables difficultés de déglutition mais ils présentaient presque exclusivement des symptômes des voies respiratoires. Les symptômes étaient très déconcertants, ils causaient des difficultés de diagnostic. L'auteur discute les 2 cas et indique, entre autres, la nécessité de radiographies avec «contrast medium» même chez les petits enfants.

Zusammenfassung

Verfasser berichtet über 2 Fälle, wo grosse Fremdkörper im Oesophagus durch 2 $^1/_2$ bzw. 3 Monate trotz wiederholter Untersuchungen nicht entdeckt wurden. Keiner der Patienten hatte bemerkenswerte Schluckbeschwerden sondern fast ausschliesslich Symptome von Seiten des Respirationstraktes. Die Symptome waren so verwirrt, dass sie zu diagnostischen Schwierigkeiten führten. Der Autor weist nachdrücklich auf die Notwendigkeit von Röntgenuntersuchungen mit Kontrastmittel auch bei Kleinkindern hin.

Resumen

El autor informa sobre 2 niños en los que los grandes cuerpos extraños quedaron sin descubrir en el esófago durante un tiempo de 2 $^1/_2$ meses a 3, respectivamente, a pesar de repetidos exámenes. Ninguno de los enfermos tenía dificultades de tragar, sino que tenían casi exclusivamente dificultades perceptibles en el conducto respiratorio. Los síntomas eran muy confusos y ocasionaban por esta razón dificultades al diagnosticar. El autor discute los dos casos y entre otras cosas recalca la necesidad de efectuar estudios roentgenográficos como medio de contraste también en los niños pequeños.

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CASE REPORTS

Forward Subluxation of the Atlas Following Birth Trauma

by

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In the following, I wish to present a case of spontaneous forward subluxation of the atlas in a newborn child treated in the Children's Clinic. The dislocation was the result of a birth trauma, and reposition was apparently spontaneous. Hitherto no similar case has been reported.

M. E. K. aged 2 months, the daughter of a lawyer. Hereditarily there was nothing noteworthy. She was the first child and born at home at full term. The delivery was tedious, the expulsive stage lasting almost 5 hours, this was evidently because of an anomaly of position; according to the mother, the head did not present until the doctor had reversed the child through a grip by the mouth. Weight at birth 3 950 gr, vital immediately. Partly breast-fed receiving supplementary formula. *Development* she sucked well and raised her head when 1 week old. According to her mother breathing was somewhat difficult, however. This was supposed to be caused by nasal catarrh, but the child did not seem to suffer from it and gained weight normally. When 4 1/2 weeks old, difficulty in breathing suddenly occurred and the child seemed to be suffocating turning violently cyanotic. Nevertheless she remained conscious. Inhalation of aqueous vapor gave relief and the attack diminished considerably in about half an hour. In the evening of the following day high fever (40.2° r) was established and breathing still remained difficult. Periodical attacks of coughing occurred in the beginning, changing after a couple of days into an irritating hacking cough, the voice at the same time becoming hoarse. The fever continued for a period of 1 week. Sulfa preparations were prescribed, then penicillin. The general condition rapidly grew worse, the temperature became subnormal, and the breathing difficulty seemed gradually to increase. The patient was admitted to the Children's Clinic on Aug. 12, 1947, 8 weeks old.

Condition on Admission. Temperature 37.2. General condition poor; the patient looked seriously ill, tired and suffering, cyanotic. Physical structure normal, nutritional condition quite poor, skin dry and peeling, elasticity reduced. The heart sounds were light and, due to the stridor, hardly audible. However, a systolic rasping sound could be heard throughout the heart, more clearly over the apex. A few bronchitic sounds, no dullness. Nervous system: no motor paralysis nor provable disturbances in the sensorium. Fully conscious. Blood count: Hb.% 75/87, E = 4.59 millions, L = 9 500, I = 0.95. SR (m) = 6/13. WaR —, Kahn —, WaR chol. —, Urine O, Feces : We —, Wa —.

Local Symptoms. The child lay with her head bent somewhat backwards, she could not raise it at all. A few enlarged lymph nodes on the front and back of the neck. The thyroid gland normal. No difficulty in deglutition. The voice somewhat hoarse, frequent, hacking cough. Marked dyspnea and cyanosis, both of which increased rapidly when she turned her head, particularly forwards. Labored breathing, snoring, and rapid the ala nasi move heavily. Extremely heavy stridor, audible during both expiration and inspiration at a distance of several meters which was also distinct during sleep. Fossa episternalis and the epigastrium were highly retracted during inspiration. Nothing noteworthy in the nose, mouth and upper part of the throat. Lower down in the pharynx, however, palpation revealed a bonehard nodule the size of half a pea protruding from its center under the mucous membrane. The tissue below the nodule felt edematous but true fluctuation could not be established with certainty owing to difficulty in palpation. *Esophagoscopy* (Professor Siirala of the Ear Clinic, Aug. 21, 1947): esophagus free. The protrusion of the larynx, the respiration and the hacking cough indicated a constriction below the glottis, and upon direct exploration a constriction of the trachea owing to a protruding posterior wall could be established. The mobility of the vocal cords was good. — *Roentgen examination* (Dr. Heikel, Aug. 18, 1947): The contrast medium made a wide forward bend at the larynx, as did the trachea. Between the esophagus and the spine there was edema of the soft parts (hematoma? abscess?). Lower down the esophagus was free. An examination of the spine revealed the dens epistrophei to be normal, in its proper place and unfractured. The atlas, however, was dislocated forward so that there was an interspace of at least 3 mm. between it and the epistropheus. For this reason the anterior arch of the atlas protruded into the posterior pharyngeal wall. No fracture of the atlas could be established, but the deficiency of lime both in the atlas and in the other upper cervical vertebrae was considerable. Roentgen diagnosis: luxatio anterior atlantidis. Haematoma (infecta?) retropharyngealis.

Course of the Disease: Treatment with penicillin, stimulants, and oxygen. On the morning of Aug. 24, 1947, there was a flow of blood-mixed

Fig. 1.

pus from the mouth of the child, the stridor was considerably eased, and the cyanosis less marked. Feces: on the next day the Weber and Wagner tests were found to be positive. In spite of slight recurring fever her general condition had evidently improved. A roentgen examination on Aug. 28th, after the end of the febrile period, revealed that the bend of the esophagus and trachea established earlier at the larynx was now much smaller, although the position of the atlas was still unchanged. The slightly subfebrile condition continued, while the stridor gradually became less marked, changing into inspiratory only and occurring intermittently. Examinations performed on Sept. 22. and Oct. 17, 1947 revealed that the nodule, which had been almost the size of a pea, had gradually diminished, being hardly palpable on the latter day. Respiration was much easier and there was snoring only in sleep Examination at the Ear Clinic (Dr. Vaheri) showed that during laryngoscopy breathing was quite unimpeded, and this fact, among other things, indicated that it was now only a question of a spastic condition in the larynx. — Due to the congenital heart disease and to some bronchopneumonic attacks, the child's general condition remained poor, however, and on Oct. 18, 1947, during the morning feeding, she suddenly became cyanotic, lost consciousness and died within a few minutes. Autopsy

on the same day revealed a defect of the intra-auricular septa. Both lungs showed small bronchopneumonic foci. The I—IV cervical vertebrae were freed. The position of the atlas in relation to the epistropheus was normal, but the ligamentum transversum which curves around the dens epistrophei was so loose that the atlas could easily be pushed forward about 4 mm. There were no signs of an effusion of blood at the insertions of the ligamentum transversum. There was, however, an evident calcium deficiency in the vertebra.

Epicrisis: The patient was 2 months old; her weight at birth was almost 4 kg. She was first child. Delivery was tedious and evidently demanded rather far-reaching medical interference. Nevertheless the child was born healthy and developed normally except for somewhat disturbed breathing which was believed to be due to a slight cold. At the age of 4 1/2 weeks she suddenly had an attack of asphyxia followed by continuous stridor, fever lasting one week and a continuous hacking cough followed by a gradual deterioration in general condition. At 8 weeks of age she was brought in poor condition to the Children's Clinic. A retropharyngeal hematoma causing typical compressional stridor and forward subluxation of the atlas was established. At the same time congenital heart disease was also established. The stridor gradually changed, due to partial emptying and partial resorption of the hematoma, into a typical spastic stridor occurring intermittently and continuing, apparently without affecting the child to any noticeable degree, until death from heart failure. Palpation, esophagoscopy and roentgen examination showed that the forward luxation of the atlas established on admission to the hospital by the same methods of examination had gradually been adjusted. This was confirmed at autopsy, as was also the correctness of the original diagnosis.

Discussion

Retropharyngeal hematoma following birth trauma and the infection and healing thereof are not very rare. I have not, however, found any case of forward luxation of the atlas as a secondary result of this process, which I venture to assert this case to be, in pediatric literature. Hence I shall relate in the

following both the anatomical and traumatological basis of such a lesion, referring, particularly with regard to the traumatology, to the very thorough and exact investigations of Watson-Jones.

The mobility of the atlas in relation to the occipital bone is limited by the soft joint capsule and also by the ventral and dorsal occipito-atloid ligaments. Most of the fibers of the former join, in their central part, the ligamentum longitudinale communis, which in newborn children is almost non-existent, the edges being attached to the aforementioned soft joint capsule. In spite of the relative firmness of its edges, the dorsal membrane cannot prevent to any great extent a forward luxation of the entire vertebra. Thus the attachment of the atlas to the occipital bone cannot really prevent forward displacement of the atlas even in an adult. As to the relation of the atlas and the epistropheus to one another, we know that the ossification of the atlas takes place as follows: the posterior arch ossificates about 2 months p. n., while the ossification of the anterior arch takes place at least half a year later. The ossification of the atlas of my patient, particularly of its anterior portion, had thus hardly begun. The common motor mechanism of the atlas and the epistropheus is based on only two factors, viz. on the ventral tension (and firmness) of the ligamentum transversum atlantis which curves round the epistropheus dorsally, and on the dorso-ventral mobility of the rather flat surfaces of both vertebrae. On this basis we may estimate the extent of the disturbance which may arise as a result of the atlas's sliding forward. We shall also find that the extent of the luxation is not decisive for the extent of the functional disturbance; witness the impossibility of nodding and raising the head when lying face downwards, as in the case described in the foregoing.

Without entering into details with regard to the traumatology of the atlas, I shall venture briefly to relate the etiology of forward luxation of the atlas. It is a fairly rare lesion of the atlas, but it is described in all more extensive works on atlas lesions (JEFFERSON, GREIG, ROBERTS, WATSON-JONES etc.). Forward luxation of the atlas is mostly partial (subluxation) and therefore, although the dens epistrophei remains uninjured, com-

pression of the spinal cord need not occur and the prognosis is accordingly favourable. A spontaneous forward luxation of the atlas may be caused by any process followed by hyperemia in the neighbourhood of the atlas, by even a slight contusion of the atlas or its surroundings or, even more frequently, by infectious processes in the tonsils or the pharynx. It is a wellknown fact that hyperemia of long duration, no matter what kind of hyperemia, causes decalcification before long (LERICHE, POLICARD). According to published reports the atlas in adults is particularly sensitive in this respect (JEFFERSON, WATSON-JONES) and, when subject to hyperemia, for instance, very soon loses its calcium to such an extent that the ligamentum transversum which curves round the dens epistropheus either becomes detached or stretched enough to allow the atlas to slide forward. In a newborn child this occurs even more readily, due to the general deficiency of calcium in the vertebrae, to the softness of the joint capsule and to the undeveloped ligamentum transversum. The ligamentum transversum, like all other joint ligaments, which in newborn children are poor in calcium, may stretch considerably without causing any notable bleeding at its points of attachment. But the reversibility should not be poorer than in the other joints of newborn children. Therefore, the calcium content gradually increases, the ligament tightens, and the joint soon returns to its proper position, particularly when the child is in a state of complete rest. At least the autopsy finding does not speak against this. Unfortunately the limpness of the child's neck was not, according to the record, tested at a later stage of the illness. Finally, since surgeons are of the opinion that reposition of a forward subluxation of the atlas is fairly easy, provided it is followed by a sufficiently long immobilization, it seems very probable that Nature could accomplish it, seeing that the circumstances are so much more favourable. My opinion is therefore that the child would probably also have coped successfully with the secondary birth complication described in the foregoing if only the hereditary heart disease had not simultaneously fatally affected the final result.

Summary

The author describes a case of a 2 month old child in which a posteriorly infected retropharyngeal hematoma following birth trauma caused a heavy laryngeal stridor and later, the stridor having lasted 4 weeks, as a secondary result a »spontaneous» forward luxation of the atlas which hitherto has not been described in a newborn child. He considers this subluxation to be caused by decalcification following infectious hyperemia. Based on the development of the disease, he establishes the reversibility of this process. At an autopsy performed immediately upon death confirmation of the diagnosis was facilitated by the presence of the hereditary heart disease.

Résumé

Cas d'un enfant de 2 mois chez lequel une hématome rétropharyngienne, provenant d'un trauma de naissance, et infectée ultérieurement, a causé une grave stridultation laryngienne et plus tard, la stridultation ayant duré 4 semaines, comme résultat secondaire, une »spontanée» luxation en avant de l'atlas laquelle, jusqu'ici, n'a pas été décrite chez un nouveau-né. L'auteur considère que cette subluxation est causée par la décalcification qui suit une hypérémie infectieuse. Se basant sur le développement de la maladie, il établit la réversibilité de ce processus. Lors d'une autopsie, faite immédiatement après la mort, la confirmation du diagnostic était facilitée par la présence de la maladie de coeur héréditaire.

Zusammenfassung

Der Autor beschreibt einen Fall eines 2 Mon. alten Kindes bei welchem ein durch Geburtstrauma entstandenes, später infiziertes retropharyngeales Haematom heftigen Larynx-Stridor und nach 4 Wochen langer Dauer desselben als sekundäre Folge eine »spontane» Vorwärts-Luxation des Atlas verursachte, wie sie bisher bei Neugeborenen noch nicht beschrieben worden war. Er betrachtet diese Subluxation als durch Entkalkung infolge einer Infektions-Hyperaemie hervorgerufen. Auf Grund des Krankheitsverlaufes stellt er die Reversibilität dieses Prozesses

fest. Bei einer unmittelbar nach dem Tode vorgenommenen Autopsie wurde die Bestätigung der Diagnose durch das Vorhandensein eines hereditären Herzfehlers erleichtert.

Resumen

El autor describe el caso de un niño de 2 meses de edad, en el que una hematoma retrofaríngea, posteriormente infectada, siguiendo a un trauma de nacimiento, causó un fuerte estridor laríngeo y más tarde, cuando el estridor había durado 4 semanas, dió lugar, como resultado secundario, a una espontánea luxación hacia adelante del atlas, lo cual no se ha descrito hasta ahora en un niño recién nacido. El autor considera que esta subluxación fué causada por descalcificación, siguiendo a una hiperemia infecciosa. Basándose en el desarrollo de la enfermedad, el autor establece la reversibilidad de este proceso. Durante una autopsia efectuada inmediatamente después de la muerte, se facilitó la confirmación del diagnóstico por la presencia de una enfermedad hereditaria cardíaca.

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Unusual Case of Anemia Gravis in a Newborn Infant[1]

by

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On November 20th, 1947, a boy seven days old was admitted from a maternity home to the Copenhagen County Hospital in Gentofte with the diagnosis anemia and jaundice. The history was as follows.

He was the third child of healthy parents; the first two children were twenty month old twins, one born with harelip and cleft palate, but otherwise both in good health and not affected by anemia or jaundice at birth. The mother had never had an abortion nor received a blood transfusion. During pregnancy her food was well varied and she took no toxic medicine.

The child was born at term and the delivery was normal. He was unaffected by the birth and was only breast-fed. On the first day of life he was jaundiced. The jaundice increased until the third or fourth day, when it was very pronounced. It had almost disappeared by the sixth day and the patient was extremely pale. As his pallor increased and he grew apathetic on the following day, he was transferred to the hospital.

Physical Examination. The patient was extremely anemic, white as a sheet, apathetic, and cool, but not jaundiced. The rectal temperature was 35.8° (Celsius).

The eyelids were slightly edematous, otherwise there was no edema. The lower pole of the spleen was palpable but apart from this the immediate physical examination was essentially negative. The child's state of nutrition and turgor was good, and there were no signs of hemorrhagic diathesis and no cerebral symptoms.

Blood Examination. Hemoglobin: 20 %. Erythrocytes: 0.52 mill. Leucocytes: 33440. Colour index: 1.8. Platelets: 342000. Icterus index (not determined until 17/12): 4. Clotting time (17/12): 1 minute 45 seconds. Bleeding time (17/12): 2 $^1/_2$ minutes. Osmotic resistance (17/12):

[1] Read before the Danish Society of Pediatrics, Copenhagen, on April 14th, 1948.

beginning hemolysis at 0.46 %, total hemolysis at 0.38 %. Wassermann: negative both in mother and child.

The bone marrow showed signs of lively regeneration with a large number of immature cells both of the white system (Table 1) and of the red system, with a large number of megaloblasts and promegaloblasts (Table 2).

The differential count on peripheral blood showed a shift to the left (Table 3).

Table 1.

Bone Marrow, the »White System«:

myeloblasts	0.50 %
promyelocytes	1.00 %
neutrophil myelocytes (1 in mitosis)	36.00 %
eosinophil myelocytes	1.50 %
basophil myelocytes	0
metamyelocytes + stab-cells	36.50 %
polymorpho-nuclears, neutrophil	6.25 %
polymorpho-nuclears, eosinophil	0.25 %
polymorpho-nuclears, basophil	0
lymphoblasts	0
lymphocytes	15.75 %
monocytes	0
plasma cells	0
megacaryocytes	0.25 %
reticulum cells	0

Table 2.

Per 400 cells of the »white system« were found:

proerythroblasts (1 in mitosis)	12
erythroblasts, basophil (2 in mitosis)	39
erythroblasts, eosinophil	77
promegaloblasts (1 in mitosis)	17
megaloblasts, basophil	25
megaloblasts, eosinophil	23

Table 3.

Differential count, peripheral blood:

neutrophil myelocytes	1.50 %
stab-cells, neutrophil	19.00 %
polymorpho-nuclears, neutrophil	16.50 %
polymorpho-nuclears, eosinophil	2.50 %
polymorpho-nuclears, basophil	0
lymphocytes	60.50 %
monocytes	0

Per 200 white cells counted were found:

1 proerythroblast
5 erythroblasts with basophil cytoplasm
5 erythroblasts with eosinophil cytoplasm.

The diameter of the erythrocytes varied from 5 to 9—10 μ. The larger erythrocytes were slightly oval and saturated with hemoglobin.

Serological Examinations

As erythroblastosis fetalis was strongly indicated by the clinical picture, bloodgrouping was made on samples from the patient, his parents, and his brothers. The tests were carried out by the Blood Grouping Department of the State Serum Institute.

Routine grouping gave the following:

Mother:	B	MN	P + + +	Rh-pos.
Father:	A_1	M	P + + +	Rh-pos.
Patient	0	MN	P + + +	Rh-pos.
Brothers (twins)	0	M	P +	Rh-pos.
	0	M	P +	Rh-pos.

Thus immunization to antigens of the AB0-, MN-, and P-systems was out of question. As immunization to the various Rh-antigens was conceivable, Rh-genotype determination was carried out with the four anti-Rh sera available. The results were as follows:

	anti-D	anti-C	anti-E	anti-c	Genes Observed	Commonest Genotype in Each Reaction group
Mother:	+	+	+	+	CDEc	CDe/cDE
Father:	+	+	÷	÷	CDeCe	CDe/CDe
Patient:	+	+	+	+	CDEc	CDe/cDE
Brothers:	+	+	+	+	CDEc	CDe/cDE
	+	+	+	+		

Thus the patient and his mother had the same Rh-antigens — at any rate the four that could be determined directly. Furthermore, no possibility of immunization was found on utilizing the results obtained for a probable genotype determination, i. e. such genotypes as are by far the most common, with the known agglutination reactions. Theoretically it was possible that the mother lacked the e-antigen and was immunized by the e-antigen present in the patient, but this possibility was contradicted by the following facts:

1) in spite of repeated examinations, it was not possible to demonstrate any anti-e in the mother's serum — not even in the incomplete form (just as the serum was examined for all known Rh-antibodies as well as anti-M, anti-N, anti-P and anti-Lewis, all with negative results),
2) the erythrocytes of the child were not agglutinated by the mother's serum. These examinations may be tabulated as follows:

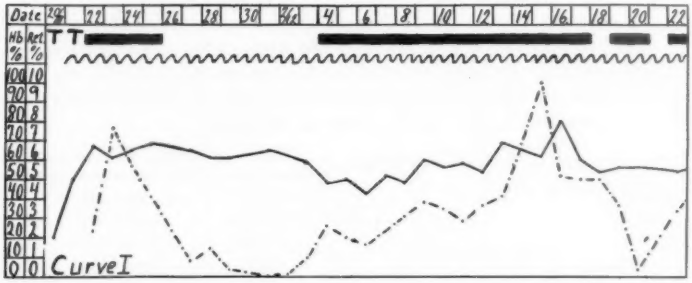
Known Erythrocytes of Group:

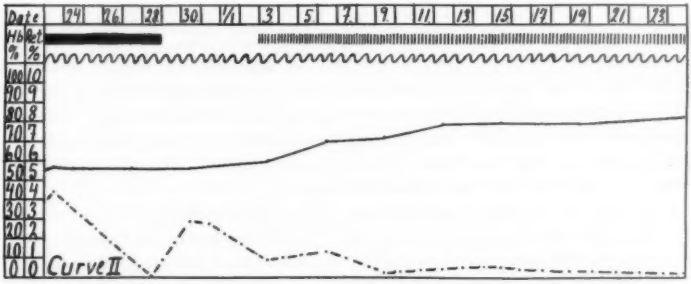
Erythrocytes Suspended in	0 M P÷ Lewis÷ Cde/cde	0 MN P(+) Lewis÷ cdE/cd	0 MN P+++ Lewis÷ CDe/cDE	0 M P++ Lewis÷ cDE/c	0 M P÷ Lewis+ CDe/cde	0 MN P÷ Lewis÷ cde/cde	0 MN P++ Lewis+ cde/cde	Pt's Erythrocytes	
Saline	÷	÷	÷	÷	÷	÷	÷	÷	20° } Mother's Serum
Saline	÷	÷	÷	÷	÷	÷	÷	÷	37° } Mother's Serum
Albumin	÷	÷	÷	÷	÷	÷	÷	÷	37° } Mother's Serum

Consequently it is most unlikely that the disease of the patient was due to any immunization to the known blood group antigens.

Treatment and Course of the Case

Curves I and II show the hemoglobin percentage and the percental reticulocyte count during the treatment.





——— = Hb%
-·-·-·- = Reticulocyte%
T = Transfusion
▬▬ = Hepsol fort
∿∿∿ = Ferrosi tartras
▒▒▒▒▒ = Ascorbic acid

On the day of admission and the following day the patient was given intratibial blood transfusions, each time 70 ml from donor group 0 (Rh-negative, as the Rh-group of the mother and child had not then been determined).

From the second day he was placed on 0.25 g ferrosi tartras daily, increasing to 0.75 g. Injectable liver extract (Hepsol fortior MCO) 1 ml was given intramuscularly on the third day and continued the following 3 days with 2 ml. From January 3rd on 0.025 g ascorbic acid was added daily. The diet was a mixture of wet-nurse's milk and mother's milk, later mother's milk supplemented with milk and barley water (50 %).

The second and third day showed a rise in the hemoglobin percentage to 50 and 67, respectively; the following 10 days it remained at 60—65, after which it showed a tendency to fall (48—43 %).

The reticulocyte count was 2.80 % on the third day, but after commencement of the Hepsol therapy on the next day it rose to 7.5 %. Later it fell to a normal level. As the hemoglobin percentage showed a tendency to fall after 10 days, treatment with Hepsol fortior was resumed and continued for about 3 weeks with a daily dose of 2 ml intramuscularly. During this treatment the hemoglobin percentage rose to about 60 (one day it showed 80 %, but probably this single high value was not reliable). After this the hemoglobin percentage remained constantly at about 55 in spite of continued administration of iron and Hepsol.

The reticulocyte count varied; generally it was increased — and once it rose to 10 %.

The Hepsol therapy was discontinued after 3 weeks, and a few days later a gradual and lasting increase in the hemoglobin percentage — up to 80 — began and the reticulocyte count decreased to normal values. The final increase in hemoglobin occurred simultaneously with the institution of ascorbic acid therapy and the complete removal of mother's milk from the diet. Subsequently we wondered whether the mother's milk contained some antibodies which might have caused the lack of increase in hemoglobin percentage. This does not seem very likely, however, as antibodies could not be demonstrated in the mother's blood; the milk was not examined.

During treatment the red and the white blood pictures gradually changed in a normal direction and the examinations on December 17th and 23rd both proved to be normal.

The child was discharged on January 28th with a hemoglobin percentage of 83. At reexamination on February 24th he was perfectly well with a hemoglobin percentage of 97, reticulocyte count 0.2 %, and normal blood picture. Furthermore, on March 13th he was again reported to be perfectly well. Throughout his stay in the hospital his temperature was normal — except for two days when the blood transfusions were followed by a slight rise.

Discussion

During the last 30 years a large number of cases of a so-called idiopathic anemia, anemia of the newborn or anemia neonatorum, sometimes accompanied by jaundice and sometimes not, and with a greater or lesser number of erythroblasts in the peripheral blood, have been described in the literature. In a few cases megalocytes have also been observed. From the case histories, especially the family histories, it is evident that a majority of these cases at any rate must have been what we now designate morbus hemolyticus neonatorum, the condition due to divergent Rh- and other blood groups in mother and child. In the case described by Bent Andersen (1936) the family history was not typical, as the patient was number five of five children, with the other children all living and well.

Since the discovery of the Rh-groups nearly all cases of morbus hemolyticus neonatorum have been interpreted as a result of immunization to the Rh- or A- and B antigens.

Potter claims that in most cases of anemia neonatorum in children of Rh-positive mothers the etiology must be another, even though in rare cases the affection may be due to different Rh-subtypes in mother and child.

In our case we have not been able to demonstrate the etiology of the anemia, which was of severe megalocytic type with signs of extramedullary erythropoiesis. The pronounced jaundice indicated a hemolytic anemia; the megalocytosis suggested possible liver damage. Syphilis and other infections, intoxication, and deficient anemia seemed to be out of question, and immunization caused by incompatible Rh- or other blood group antigens seemed very unlikely on the basis of the serological examinations.

Summary

A case of severe megaloblastic anemia (hemoglobin: 20 %) in a 7 day old boy is described. The etiology is unknown. Blood group incompatibility cannot have been the cause, as mother and child were both Rh-positive with identical Rh-genotypes and the child belonged to group 0. Intoxication as well as syphilis and other infections seemed to be out of question.

Blood transfusions were effective, whereas the effect of liver therapy was not convincing. The child recovered in 2 months.

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Akute Appendicitis bei einem 3 Wochen alten, frühgeborenen Kinde

von

C.-G. ENGSTRÖM

Aus dem Sach'schen Kinderkrankenhaus, Stockholm
(Chefarzt: Docent J. Henning Magnusson)

Die Appendicitis ist im frühesten Kindesalter ein seltenes Krankheitsbild. Dies gilt besonders für Neugeborene und in den ersten Lebensmonaten stehende Kinder. Zur Bestätigung dieser Auffassung kann auf die grossen Reihen von Appendicitisfällen bei Kindern hingewiesen werden, die von verschiedenen Verfassern veröffentlicht wurden. So stellte Busch und sein Mitarbeiter als jüngsten Patienten in einer Serie von 635 Fällen ein 18 Monat altes Kind fest. Ähnliche Veröffentlichungen, wie von Allen über 612 Fälle und von Hudson und Chamberlain über 848 Fälle berichten jeweils über nur einen Fall im ersten Lebensjahr. In Norris Zusammenstellung von 1000 Fällen wird das Alter des jüngsten Patienten mit 4 Monaten angegeben. Bei den von Edberg veröffentlichten 754 Fällen scheinen 3 unter einem Jahr alt gewesen zu sein. Dass indessen die Appendicitis eine Erkrankung ist, die jederzeit im frühesten Kindesalter, ja sogar praenatal auftreten kann, geht aus der Literatur hervor. Eine geringe Zahl praenataler Appendicitisfälle und Appendicitisfälle bei Frühgeburten und Neugeborenen sind veröffentlicht worden (Lilienthal, Hill, Corcoran, Jackson).

Im Sachs'schen Kinderkrankenhaus wurde Herbst 1948 ein 3 Wochen alter vorzeitig geborener Junge mit einer akuten phlegmonösen Appendicitis behandelt.

Junge H. geboren den 24.9. 1948. Krankenjournal N:o 754/48. Wegen Debilitas vitae congenita Verlegung von der Entbindungsabteilung des Söder-krankenhauses nach dem Sach'schen Kinderkrankenhaus. Gewicht bei der Geburt 1290 g. Mutter 20 Jahr, unverheiratet, primipara, kein Abort. Kurz vor der Aufnahme in die Entbindungsabteilung des Söder-krankenhauses entbunden. Angeblich war Gravidität und Partus ohne Komplikation.

Status (bei der Aufnahme in's Sach'schen Kinderkrankenhaus) den 24.9. 1948: Ausgesprochenes debiles Kind mit ziemlich schwachem Schrei, gewöhnliche debile Farbe, keine Cyanose. Hämatome an beiden Plantae. Die Haut ist relativ gut mit Fett unterpolstert. Skelett o. B. Die grosse Fontanelle ist für eine Fingerkuppe offen, nicht gespannt oder eingesunken. Kopfumfang: 26 cm, Brustumfang: 23 cm, Körperlänge: 37 cm, Rachenraum: o. B. Cor, Pulm., Abdomen: o. B. Blut: Hgb 135 %, rote Blutk. 6,12 Millionen. Protrombinindex: 97. Therapie: Sauerstoffcouveuse, Sondenernährung, im Bedarfsfalle Stimulantia. Ernährung: 6 mal Muttermilch in steigender Menge und 2 g Aminosol pro Kilo Körpergewicht.

Klinischer Verlauf:

Erste Lebenswoche. Leichtes Erbrechen. Bei der Ernährung tritt ab und zu Cyanose auf, mitunter gute Farbe und relativ guter Allgemeinzustand. Temp.: wechselnd, anscheinend verursacht durch den Brutschrank. Stühle: o. B. Gewichtskurve: nicht bemerkenswert.

Zweite Lebenswoche. Allgemein verschlechtert. Schnupfen und lose Rasselgeräusche über den Lungen als Zeichen einer Infektion. Die Stuhlentleerungen werden locker und schleimig. Einige Male treten Asphyxieanfälle auf, sodass der Pat. moribund erscheint. Die Gewichtskurve zeigt eine befriedigende Zunahme. Behandlung: Penicillin 8 × 2500 I E i. m. Nicetamid und Lobelin bei Bedarf. Blutinjektionen i. m. Nach einigen Tagen tritt eine deutliche Besserung ein, die Stühle werden fester und weniger schleimig, das Erbrechen verschwindet. Am Ende der 2. Woche ist der Allgemeinzustand wieder relativ gut.

Dritte Lebenswoche. In den ersten Tagen keine wesentliche Zustandsänderung. Bei der Morgenvisite am 12.10. wurde indessen eine markante Veränderung wahrgenommen. Pat. ist apathisch, zeigt verringerten Tonus und blass cyanotische Färbung. Der Leib, der bereits vorher schon Zeichen eines leichten Meteorismus aufwies, ist nun aufgetrieben und gespannt und ein rechtseitiger Leistenbruch, der schon früher hervorgetreten, aber leicht reponibel war, fühlt sich nun geschwollen und fest an und kann nicht ohne Weiteres reponiert werden. Gleichzeitig tritt während des Vormittags stärkeres Erbrechen auf. Da die Gefahr einer Incarceration besteht wird ein Chirurg hinzugezogen, dem es gelingt den Bruch zu reponieren. Auf Grund der verdächtigen abdominellen Symptome wird der Pat. am gleichen Tage in die chirurgische Kinderabteilung zur weiteren Beobachtung verlegt. Während des Aufenthalts

dort vom 12.10—15.10. verbessert sich der Zustand des Patienten nach Behandlung mit Flüssigkeit und Plasmainfusionen. Eine Indikation von Seiten des Abdomens für einen chirurgischen Eingriff ist nicht ersichtlich.

Vierte Lebenswoche. Am 15.10. 1948 in's Sachs'schen Kinderkrankenhaus zurückverlegt. Die ersten Tage nach der Rückkunft relativ guter Allgemeinzustand. Die Darmentleerungen etwas locker und schleimig, jedoch kein Erbrechen. Der Leib zeigt Meteorismus, ist aber weich. Der Bruch tritt ab und zu heraus. Das Serumeiweiss, das in der letzten Zeit trotz Plasmazufuhr und später täglichen Aminosolglykosinfusionen etwas niedrig war, sinkt weiterhin stark und beträgt am 16.10. 4,1%. Am 18.10. verschlimmert sich der Zustand des Pat. rasch. Apathisch, schlechter Tonus und blasse Hautfarbe. Der Leib ist stark aufgetrieben. In der Bauchwand und im Skrotum starke Ödeme. Nach Injektionsstichen treten Blutungen auf. Der Protrombinindex, der anfangs normal war, zeigt keine Koagulation. Nach Einlegen einer Kanüle in die Vena saphena magn. erhält der Pat. 35 ml Blut, kommt jedoch kurz nach der Transfusion ad exitum.

Obduktionsbericht. (Med. Dr F. Wahlgren): Nicht voll ausgetragenes Kind mit bleicher Hautfarbe. Der Leib ist aufgetrieben und gespannt. Rechtseitiger Leistenbruch. Das Herz und die grossen Gefässe zeigen keinerlei Missbildungen oder andere Veränderungen. Die Lungen waren hauptsächlich in den vorderen Teilen lufthaltig, während die hinteren Teile sich in grossem Umfang atelaktisch und blutreich erwiesen.

Keinerlei Fremdkörper in der Trachea oder den Bronchen.

Die Schleimhaut war blass.

In der Bauchhöhle fand sich eine geringe Menge klarer Flüssigkeit.

Das Peritoneum war glatt und glänzend. Ventrikel, Dünndarm und Colon ascendens waren vom Gasdruck stark ausgedehnt und gespannt. Die Schleimhaut war blass. Der Appendix lag als ein Korkzieherartiges Gebilde auf der Medialseite des Coecums, das auffällig rotbraun missgefärbt war, jedoch keinen Fibrinbelag auf seiner Serosa zeigte. Der Leber hatte normale Grösse und war von gewöhnlicher fester Consistens und zeigte rotbraune Schnittfläche.

Gallenwege, Pankreas und Vena Portae o. B.

Die Milz hatte normale Grösse und Consistens und zeigte dunkelrote Schnittfläche.

Nebennieren o. B.

Nieren und Harnwege o. B.

Vorläufige pathol. anatom. Diagnose: Debilitas congenita—Atelectasia partialis pulmonum—Appendicitis acuta?—Hernia inguinalis dext.

Ergebnis der mikroskopischen histologischen Untersuchung: Innerhalb des Spitzenteiles des Appendix zeigt sich eine Schleimhautnekrose und reichliche Leukocyteninfiltration der Wand. Das Lumen ist mit Leukocyten gefüllt.

Pathol. anatom. Diagnose: *Akute phlegmonöse Appendicitis.*

Die übrigen untersuchten inneren Organe waren ohne Besonderheiten.

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A.-B. STILLE-WERNER · STOCKHOLM 4

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(FROM THE CHILDREN'S DEPARTMENT, UNIVERSITY HOSPITAL, LUND.
HEAD: PROFESSOR S. SIWE, M. D.)

Studies of a Toxoplasmotic Family.

Sulfathiazole Prophylaxis.

By

GUNNAR ENGLESON.

As is known, toxoplasmosis occurs in a subclinical form, in which the presence of neutralizing antibodies in the blood is the only sign of the disease. This inapparent form may be pre-existent in mothers and other relatives of children suffering from toxoplasmosis. In such a family the risk that subsequent children will acquire clinically demonstrable toxoplasmosis is regarded as rather small, though it does undoubtedly exist (1).

The writer has given an account earlier (2) of a case of toxoplasmosis in a 2 1/2 year old girl who is still living and whose parents and maternal grandmother had antibodies against toxoplasma in their blood. At the time of the examination the mother of this patient was pregnant again, and it was decided that she should be treated with sulfathiazole with a view to mitigating or preventing an intrauterine toxoplasma infection of the foetus. Earlier reports of the results obtained with such treatment are scanty. Experience from animal experiments suggests that preparations belonging to the sulfonamide group have toxoplasmicidal properties (3). JOHNSSON (4) and associates have described a case in which sulfonamide therapy was tried during pregnancy, the subject being a woman who had clinical toxoplamosis with retinochorioiditis. No effect on the ocular changes could be observed, but abortion had to be performed to preserve the patient's sight. The data concerning the placenta and foetus are incomplete. It would therefore perhaps not be out of place to submit a short report of the following case.

Case Report. — The mother was treated with sulfathiazole in a »pneumonia dose» (4 g + 4 g + 1 g × 6) 1 week per month during the last 5 months of her pregnancy. No complications supervened. — Boy born April 29, 1948. Normal delivery. Birth wt.: 3 330 g; length 53 cm; skull circumference 35 cm. Status April 30, 1948: internal organs: nothing abnormal; fundi oculi: normal; *X*-ray of cranium: no intracranial calcifications.

Examination at age of 4 months: Normal development. Breast-fed infant of normal size for his age. Weight 6 600 g. Followed movement with his eyes, laughed and raised and balanced his head. No cranial deformity. The fontanelle normal. Internal organs: nothing pathological. Fundi oculi: normal. A second x-ray examination of the cranium disclosed no intracranial calcifications. Lumbar puncture showed normal conditions. Wassermann test: negative.

Re-examination at the age of 7 months: Weight 8 700 g. Sat up without support. Roentgenograms of the skull, renewed examination of the eyes and of lumbar fluid all revealed a normal picture.

The patient was examined again at the age of 9 1/2 months: Wt. 9 kg, development still normal. He could now support himself on his legs. Fundi oculi: normal. Radiogram of the cranium displayed no calcifications. Lumbar puncture: 5.3 cells per mm^3. Nonne-Apelt and Pandy reactions: normal; Bisgaard 1: 10.

Serologic Examination. Blood specimen taken from the umbilical cord at parturition was examined for the presence of neutralizing antibodies (Dr. L. Alm, Sahlgrenska Hospital, Bact. Dept., Gothenburg). In rabbits the serum neutralized 5—10 reactive doses. The corresponding chick embryo neutralization was log. — 1.5, i. e. about 32 reactive doses. Strongly positive neutralization test. The high titer of neutralizing antibodies persisted at the same elevation when the infant was 4 months of age. A new specimen was taken and tested when the child was 7 months old. When tested on the rabbit no neutralization was found, while on chick embryo there was neutralization of only 4 reactive doses, which is not considered positive. The last examination for the presence of neutralizing antibodies was made when the patient was 9 1/2 months old, when the test was completely negative. On this occasion the mother's serum reacted strongly positive to the neutralization test.

Examination of Placenta. At parturition a specimen of the placenta was taken for cultivation purposes. No toxoplasmotic strain could be isolated (Dr. L. Alm). X-ray examination of the placenta revealed an abundance of diffuse calcifications in the whole of the placenta. Patohistological examination (Prof. J. Mellgren). Small specimen of placenta with umbilical cord insertion showed no gross changes, but extensive micropathologic alterations. In the spaces between the villi there were

fibrin deposits with rather abundant polymorphonuclear leucocytes and a few single scattered macrophages as well as an abundance of other small bodies, some of which were obviously nuclear fragments 5—10 μ in size, while others were much smaller and of rather uniform size, 2—4 μ. Some of the clumps of these last-mentioned bodies were darker at one end, very scanty comma-shaped protoplasm. No clear-cut necrosis. No infarcts. The picture resembled that seen in the placenta of an earlier patient with toxoplasmosis. Here, however, the changes were more extensive and bodies suggestive of toxoplasmosis were far more abundant, but on the other hand, necrosis was absent and there was no purulent infiltration. Probable diagnosis: toxoplasmosis.

Discussion.

Serologic examinations showed that neutralizing antibodies against toxoplasmosis are capable of passing from the mother's blood into the foetus and that the titer of the neutralizing antibodies, which may thus arise in the infant, may persist until 4 months after delivery. In addition hereto, this infant did not react to the neutralization test at the last 2 examinations, when he was 7 and 9 months old. This child thus escaped toxoplasmosis. As experience has shown that almost all brothers and sisters of toxoplasmotic children have neutralizing antibodies in the blood and thus have subclinical toxoplamosis, there is reason to believe that in this case sulfatiazole treatment of the mother during pregnancy had an inhibitory effect on the toxoplasmosis.

Summary.

A woman who had previously given birth to a child with toxoplasmosis was again pregnant. Sulfatiazole prophylaxis was given. The child did not develop toxoplasmosis.

Résumé.

Une femme qui avait donné naissance auparavant à un enfant atteint de toxoplasmose, était de nouveau gravide. Un traitement prophylactique au sulphatiazol fut administré. La toxoplasmose ne se développa pas chez l'enfant.

Zusammenfassung.

Eine Frau, die vorher ein Kind mit Toxoplasmosis geboren hatte, war wieder schwanger. Es wurde Sulphatiazol-prophylaxe durchgeführt. Das Kind bekam keine Toxoplasmosis.

Resumen.

Una mujer que había anteriormente dado a luz un infante con toxoplasmosis, se encontraba de nuevo en estado de pregnación. Se le suministró sulfatizol como profilaxis. Al nuevo hijo no se le presentó toxoplasmosis.

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Further references: see No. 2.

Le zona ophtalmique chez l'enfant

par

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Déjà au début de notre ère on connaissait le zona et il avait été décrit par les savants de cette époque, entre autres par Celse. Cette maladie n'a cessé depuis lors d'attirer sur elle une attention toute particulière. Après plusieurs siècles de recherches à l'aveugle, ce n'est guère que depuis une centaine d'années que la science a réussi à résoudre un grand nombre des points obscurs que présentait cette maladie, mais il reste encore à éclaircir beaucoup de questions. A cet égard il y a lieu de nommer von Bärensprung qui signala vers les années 1860 la relation existant entre le zona et le système nerveux, en particulier les ganglions spinaux. C'est à peu près à la même date que remonte la conception du »zona ophtalmique». Il y a tout lieu de supposer que le zona de la face s'est présenté aussi longtemps qu'il y a eu des cas de zona en général. Il semble qu'on n'ait pas considéré ces cas comme des cas de zona, mais qu'on les ait classés sous une autre rubrique et qu'en général on les ait considérés comme une forme d'érysipèle, sort qui fut réservé pendant certaines époques à tous les zonas. Après que Hutchinson eut éclairci en 1866 ces conceptions et eut publié plusieurs cas de zona ophtalmique, on trouve une plus abondante littérature médicale dans ce domaine.

Il semble que les cas de zona de la face aient été rares, tout au moins jusqu'à la fin du siècle dernier. Dans sa thèse, soutenue en 1869, Jacks passe en revue tous les cas publiés jusqu'alors, au nombre de 50, et présente pour sa part un cas, le cinquième observé en Allemagne. En 1871, dans sa thèse sur le même sujet, Kocks présenta les cas survenus ultérieurement. Avec ceux dé-

crits précédemment, cela en présentait alors un total de 80. L'indication de l'âge figurait dans 71 cas, dont 5 tombant dans le groupe des malades âgés de 1 à 10 ans. Chez les deux auteurs précités, comme chez d'autres des auteurs antérieurs, on trouve plusieurs cas de zona ophtalmique chez l'enfant sans qu'ils soient considérés comme quelque chose de remarquable. En examinant avec discernement les renseignements qu'on trouve sur ces cas, on ne peut s'empêcher de penser que dans quelques-uns d'entre eux il s'agissait d'un zona symptomatique. C'est ainsi qu'on trouve quelquefois qu'il s'agissait d'un mauvais état général, d'un trauma de la tête, ou que le zona était bilatéral, renseignements qui confirment l'existence de la maladie soupçonnée plus haut.

Peu à peu les enfants disparurent pour ainsi dire complètement dans les ouvrages traitant des cas de zona ophtalmique et l'on se mit à décrire des cas isolés chez l'enfant en les présentant comme très rares. La littérature médicale traitant de ces cas n'est guère voluminuese jusqu'à présent. Bonar et Pearsall ont constaté cette maladie chez un enfant de 4 jours. Lomer cite deux cas observés par Bohn: dans l'un il s'agissait d'un enfant de 5 mois et dans l'autre de 7 mois. Ces trois cas paraissent être les seuls cités chez des enfants aussi jeunes. On ne trouve malheureusement que peu de renseignements sur ces cas. En 1907 Rachmaninow a décrit en détail un cas de zona ophtalmique chez une petite fille âgée de 4 ans et demi. Un trauma de l'occiput, bien que de caractère bénin, avait précédé la maladie. Le tableau qu'il a donné de celle-ci était assez caractéristique, sauf que les prodromes furent nettement prononcés et durèrent longtemps et que les douleurs continuèrent même après le décollement des croûtes, ce qui ne correspond nullement à l'évolution habituelle de cette maladie chez l'enfant. L'oeil ne paraissait pas avoir été atteint. En 1920 Rollet et Bussy ont décrit un cas chez une fillette de 10 ans. Il s'agissait d'un cas nettement bénin et sans complications oculaires. Ces auteurs mentionnent quelques traits caratéristiques du zona chez l'enfant. En 1928 Mc Murray déclare que le zona ophtalmique est »an exceedingly rare condition in infancy». Il n'en avait pas trové de décrits précédemment en

Amérique. Lui-même en décrit un. Il s'agit d'une petite fille âgée de 15 mois. L'évolution de la maladie fut particulière en ce qu'elle débuta par une adénite suppurante du cou. Une affection de la peau de la face survint environ une semaine plus tard et fut considérée comme un cas d'érysipèle, mais prit après quelques jours l'aspect caractéristique du zona ophtalmique. La cornée ne fut pas atteinte. En 1939 Koch a décrit un cas de zona ophtalmique chez un petit garçon de 5 ans et demi et il ajoute que le plus jeune malade chez lequel un cas eût été constaté jusqu'alors à la Clinique Mayo était un enfant de 12 ans. Quelques autres auteurs ont également observé des cas de zona ophtalmique chez l'enfant, mais il n'en sera pas fait mention ici. Les traités d'ophtalmologie et de dermatologie parlent très peu ou pas du tout du zona ophtalmique chez l'enfant. »Der Herpes Zoster ophtalmicus kommt in jedem Lebensalter vor». Cette phrase, qu'on trouve déjà chez les premiers auteurs, revient souvent dans la littérature médicale. Les ouvrages traitant des maladies des enfants ne disent en général rien de la fréquence de cette forme du zona chez l'enfant. Ils se contentent en général de signaler qu'on rencontre cette forme de la maladie et la considèrent comme grave. Cependant Lehndorff, en parlant dans son manuel »Handbuch der Kinderheilkunde» du zona de la face, dit n'avoir trouvé que quelques cas décrits chez l'enfant. Lodge et Lodge citent dans un article publié en 1923 un propos intéressant de Henry Head: »Herpes zoster in children is almost a negligible disease. Were it not that the mothers are frightened of the rash we should see very few cases in young persons. The elasticity of the ganglia and surrounding parts probably provents the occurrence of severe forme of pain. Notoriously, herpes zoster wherever it occurs is much more severe in old people than in young. This is particularly the case when the rash lies over the forehead». Il ressort donc de ces lignes que l'infection zostérienne chez l'enfant n'est accompagnée que de très légères douleurs ce qu'on constaterait aussi dans le zona ophtalmique. On peut, en outre, en conclure que le zona chez l'enfant n'est peut-être pas aussi fréquemment l'objet d'un traitement médical que le zona chez l'adulte. Tel n'est sûrement pas le cas, tout au moins

en ce qui concerne le zona ophtalmique. Ce n'est pas la douleur qui incite à recourir au médecin, mais l'éruption et, avant tout, l'immanquable enflure de la paupière qui, en général, est considérable. Je dirai même que le zona ophtalmique est le type de zona qui est le plus souvent l'objet d'un traitement médical. On aurait donc peut-être tendance à exagérer la fréquence de cette forme de zona comparativement aux autres formes.

J'ai eu l'occasion d'observer et de suivre deux cas de zona ophtalmique chez l'enfant. J'ai été intéressé par conséquent de savoir quelle était la fréquence de cette maladie chez l'enfant. Pour être fixé sur cette question, j'ai étudié toutes les fiches d'observations de cas de zona que j'ai trouvées dans deux des plus grandes cliniques ophtalmologiques de Suède: celle de l'Hôpital Carolin de Stockholm et celle de l'Hôpital Sahlgren de Göteborg. Il en ressort que le zona ophtalmique doit être une maladie rare chez l'enfant. Les indications que nous trouvons à ce sujet en Amérique, et dont j'ai parlé plus haut, le montrent clairement. Le zona est une maladie infectieuse et comme telle elle est soumise à des variations de fréquence, à des degrés de complication, etc. C'est pourquoi à des périodes différentes ou dans un autre lieu géographique il peut évidemment se présenter d'une manière toute différente. Ayant eu à ma disposition une assez grande quantité de fiches d'observations relatives au zona, j'ai estimé qu'il valait la peine de les étudier de plus près.

Ces fiches comprenaient tous les cas de zona ophtalmique des malades hospitalisés ou consultants qui ont été traités dans les deux cliniques mentionnées plus haut pendant les années 1935 à 1947. Ont été seuls pris en considération les cas de zona déclaré, c'est-à-dire ceux présentant des manifestations caractéristiques de la peau. Les cas traités, par exemple, pour névralgie consécutive au zona ou pour complications oculaires persistantes ont, par conséquent, été éliminés. L'ensemble des fiches d'observations concernait 291 cas que j'ai répartis, tenant compte de l'âge des malades au début de leur maladie, en groupes qui ont servi de base pour l'établissement d'un diagramme (voir figure 1) montrant la répartition de ces cas suivant l'âge. Ce diagramme est très intéressant. Il y a lieu de signaler à cette occasion que deux

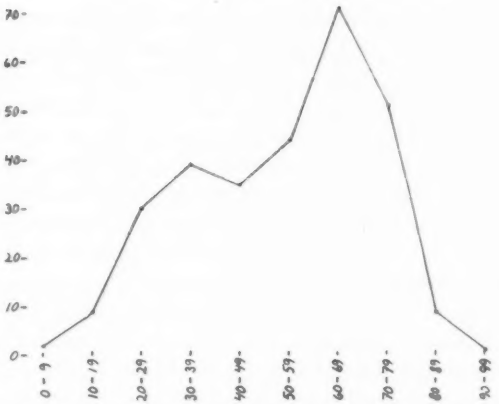

Diagramme montrant la répartition des cas de zona ophtalmique suivant l'âge des malades. Sur l'axe des abscisses: âge des malades, par groupes de dix ans. Sur l'axe des ordonnées: nombre des cas.

cas seulement — celui d'un petit garçon d'un an et celui d'une petite fille de six ans — tombent dans le groupe de 0 à 9 ans. On trouve un cas encore parmi les enfants âgés de moins de 15 ans, c'est celui d'un petit garçon de 12 ans.

Les principaux traits de l'évolution clinique du zona sont identiques, quel que soit le lieu de localisation de la maladie, et peuvent être résumés comme suit. La période d'incubation est en général d'une à deux semaines. La maladie débute par une phase préliminaire caractérisée par un malaise général, de la fièvre, de vagues douleurs articulaires et musculaires et des douleurs névralgiques dans la région de la future éruption. Cette phase préliminaire est d'une durée très variable, allant de quelques heures à plusieurs semaines. L'éruption débute ensuite. Elle est précédée d'un oedème rosé sur lequel apparaissent des bouquets de papilles coloriées. Au début, et surtout dans le zona de la face, la ressemblance avec l'érysipèle peut être frappante. Les papilles se transforment en général en vésicules dont le contenu se trouble rapidement et qui, après 2 à 3 jours se dessèchent en formant des croûtes. Pendant les jours suivants apparaissent de nouveaux bouquets de vésicules, de sorte qu'on peut voir en même temps,

l'une à côté de l'autre, des vésicules à des phases différentes de leur évolution comme c'est le cas dans la varicelle. Les croûtes tombent au bout d'une à trois semaines laissant généralement des cicatries qui souvent ne disparaissent pas. La fièvre se manifeste quelquefois pendant les premiers jours de la maladie et tombe d'habitude après l'éruption des vésicules. Les glandes lymphatiques tributaires du territoire envahi sont toujours enflées et sensibles. Les douleurs névralgiques se manifestent très tôt et sont ordinairement le plus douloureux et le plus grave des symptômes habituels. Ces douleurs peuvent prendre le caractère de fortes névralgies ne cessant pas avec la disparition de l'éruption et peuvent même continuer longtemps. Il se produit quelquefois aussi, à côté des altérations des nerfs sensitifs, des troubles des nerfs moteurs, par exemple des nerfs faciaux, lors d'un zona de la face.

Le zona ophtalmique suit de près l'évolution qui vient d'être décrite. Il y a lieu d'indiquer ici quelques traits caractéristiques qui le différencient des autres formes de zona, Somme toute, le zona ophtalmique est plus grave. L'état général du malade est plus fortement touché. Les vesicules sont souvent hémorragiques ou gangréneuses, laissant par suite après elles de vilaines cicatrices. Les névralgies sont de règle et sont souvent particulièrement douloureuses. Dans son traité dans »Handbuch der Haut- und Geschlechtskrankheiten», W. Schönfeld dit à leur sujet: »Sie können sich bei jeder Form des Zoster finden, am regelmässigsten beim Zoster ophtalmicus, hierbei in jedem Lebensalter». Evidemment, en raison de sa relation avec l'oeil, le zona ophtalmique occupe une place spéciale. En général, on estime que plus de la moitié des cas sont accompagnés de complications oculaires. Il s'agit le plus souvent de kératite superficielle ou profonde, parfois d'iritis, de névrite oculaire, de glaucome ou d'autres complications. Ces complications peuvent survenir dans les différentes phases de la maladie.

Le zona chez l'enfant a généralement une évolution bénigne. Les douleurs sont faibles. L'éruption cutanée, qui a le même aspect caractéristique et évolue de la même façon que chez l'adulte, n'est d'habitude pas si irritante, c'est-à-dire que la sensation

de brûlure et d'élancements dans l'épiderme, qui a donné à la maladie son nom classique de »ignis sacer», fait complètement défaut. Il ne se produit point de douloureuses névralgies. L'enflure des glandes lymphatiques est assez fortement prononcée chez l'enfant. La plupart des cas de zona chez l'enfant ne montrent donc pas d'autres signes évidents de la maladie que l'éruption cutanée. Celle-ci, en outre, après guérison ne laisse presque jamais aucune cicatrice.

On peut se demander évidemment si ce qui vient d'être dit plus haut au sujet du zona chez l'enfant est applicable également quand il s'agit de zona ophtalmique. Si l'on examine tous les cas décrits dans la littérature médicale, on voit que ceux-ci sont assez bénins, mais ordinairement ne se passent pas sans incommoder plus ou moins le malade. Il a été dit précédemment que les névralgies, quand il s'agit de zona ophtalmique, se manifestent aussi chez l'enfant, ce qui se trouve confirmé dans la plupart des cas, mais elles ne semblent pas avoir été très graves. La fièvre a été forte et les adénites très souvent prononcées. Les complications oculaires, ont eu lieu, semble-t-il, à peu près dans la même proportion que chez l'adulte, mais je n'en ai pas trouvé de très graves.

Pour mettre encore plus en lumière la question de l'évolution clinique du zona ophtalmique chez l'enfant, je vais exposer maintenant les cas notés dans les fiches d'observations dont j'ai parlé plus haut.

Dans la catégorie des malades âgés de plus de 10 ans mais n'ayant pas encore atteint l'âge de 15 ans il ne se présente qu'un cas, celui d'un garçon de 12 ans, dont voici la description sommaire:

Roland K., 12 ans. — Admis dans le service des maladies des yeux de l'Hôpital Sahlgren le 14 mai 1941, sorti de l'Hôpital le 22 mai. Diagnostic: zona ophtalmique du côté gauche. Précédemment bien portant. Depuis le 9 mai, vésicules au front et légère rougeur à l'oeil gauche. N'a pas eu de douleurs. Etat le 14 mai: état général bon. Zona typique avec grosses vésicules sur la moitié gauche du front et sur la paupière supérieure gauche. En avant de l'oreille gauche, une glande lymphatique de la grosseur d'un petit pois; quelques glandes de la grosseur d'une noisette sur le côté gauche du cou. L'examen des yeux montre que l'oeil droit est indemne. A l'oeil gauche on constate une légère rougeur près de la périphérie

de la cornée, vers le bas de la partie nasale. Les parties transparentes de l'oeil sont claires et le fond de l'oeil normal. L'acuité visuelle de chacun des yeux était à peu près de 5/5 avec —0,75 cyl. à 90°. A la sortie de l'hôpital l'affection cutanée était pour ainsi dire guérie. Les yeux ne présentaient rien de particulier à noter.

En parcourant les fiches, j'ai trouvé encore un cas de zona chez un garçon de 12 ans. Ce cas ne devrait peut-être pas être mentionné ici. Il s'agissait, en effet, d'un des cas très rares oú la deuxième branche principale du trijumeau était seule engagée. La région d'innervation du rameau ophtalmique était par conséquent entièrement indemne. La maladie semble avoir été bénigne et ne nécessita pas l'hospitalisation du malade qui ne fut traité que par consultations.

Parmi les 291 cas de zona, il n'y en a que deux d'enfants âgés de moins de 12 ans, à savoir — ceux que j'ai eu l'occasion de suivre moi-même. Ces deux cas ont été traités en 1947 dans le service des maladies des yeux de l'Hôpital Carolin de Stockholm.

Nils Olov L., 18 mois. — Parents bien portants ainsi que son frère âgé de 8 ans et sa soeuer âgée de 12 ans.

Accouchement normal. Poids à sa naissance 3,990 kg. Nourri au sein jusqu'à l'âge de six mois. Constitution normale. Quand il avait un peu plus d'un mois, son frère et sa soeur ont eu une varicelle d'un aspect typique. Lui-même n'a eu qu'un seul bouton, sur une jambe. N'a pas du tout été indisposé. N'a subi d'ailleurs aucune maladie à l'exception de légers rhumes de cerveau, deux ou trois fois. Ces temps derniers ni lui ni son frère et sa soeur n'ont été atteints de maladie infectieuse. Un petit garçon du voisinage, âgé de 10 ans, avait joué avec l'enfant le 13 et le 14 octobre. Celui-là tomba malade quelques jours plus tard et le 19 octobre on put constater avec certitude qu'il avait la varicelle.

Le 16 octobre la mère découvre chez son enfant une petite vésicule au front, à la naissance des cheveux. Le lendemain, plusieurs vésicules sur le côté gauche du front. Le 18 octobre enflure des paupières de l'oeil gauche accompagnée d'une vésicule sur la paupière supérieure. L'enfant avait été un peu difficile, mais ne paraissait pas être indisposé. La température n'avait pas été prise. Le 20 octobre la mère porte son enfant à la consultation de l'Hôpital Carolin. L'enfant est admis dans le service des maladies des yeux.

A son admission, l'enfant présente un bon état général. Il ne semble nullement indisposé. Il est développé normalement pour son âge, tant physiquement que psychiquement. Taille: 84 cm. Poids: 12,5 kg. L'exa-

Fig. 1. Nils-Olov L., âgé de 1 an et demi.

men physique ordinaire ne décèle aucune affection des organes internes. L'analyse du sang montre un nombre normal des globules rouges et blancs. La teneur en hémoglobine est normale. Le décompte différentiel des globules blancs indique une valeur normale pour son âge.

S. R.: 15 mm/1 heure (méthode micrométrique). Réaction Wassermann du sang — négative. Réactions Heller et Almén de l'urine — négatives. La face montre un zona typique avec croûtes et vésicules sur la partie gauche du front, la paupière supérieure et la partie supérieure du dos du nez. Les croûtes et les vésicules empiétaient sur le cuir chevelu jusqu'au vertex. L'infection respectait la ligne médiane d'une façon caractéristique; (son aspect, au moment de l'admission de l'enfant à l'hôpital, est représenté par les photographies reproduites ici). Aucune efflorescence n'a pu être décélée dans la cavité buccale, le nez ou le canal auditif. Une glande lymphatique de la grosseur d'un petit pois était palpable en avant de l'oreille gauche. Deux glandes du cou étaient légèrement enflées. L'enflure des paupières ne permettait pas d'ouvrir l'oeil spontanément. La conjonctive était légèrement rosée et un peu pâteuse. La face interne de la paupière supérieure n'a pu être examinée qu'imparfaitement; elle ne présentait aucun signe d'infection zostérienne. La cornée était entièrement indemne. La pupille était aussi grande que celle de l'oeil droit et réagissait normalement à la lumière. Les parties internes de l'oeil étaient normales. Après l'admission de l'enfant il n'est pas survenu de nouvelles vésicules. Jamais aucune éruption sur le corps. Après deux à trois jours les croûtes se mirent à tomber et le jour de sa sortie de l'hôpital, le 25 octobre, neuvième jour après l'apparition de la première vésicule, il ne subsistait que quelques croûtes. Pendant son hospitalisation l'enfant s'est montré plein de vigueur, frais et dispos,

Fig. 2. Anita P., âgée de 6 ans.

et ne s'est jamais plaint d'aucune douleur. La température a tout le temps été de 37.2° à l'exception du jour de sa sortie de l'hôpital où elle est montée à 37,6°. Ce jour-là l'enfant était enrhumé et avait eu des selles sans consistance. Il s'agissait probablement d'une petite infection qui n'avait rien de commun avec la maladie traitée. Les examens quotidiens ont montré que l'oeil n'avait pas été atteint. Une semaine plus tard, la peau était complètement nette à l'exception de quelques taches insignifiantes d'une pigmentation anormale et présentant une surface légèrement écaillée. Rien à signaler en ce qui concerne les yeux.

Anita P. — 6 ans. — Antérieurement, somme toute, bien portante. N'a pas eu la varicelle. Cette maladie a sévi dans les environs, mais la petite n'a pas été en contact avec des malades. Le 13 janvier, plusieurs petits boutons à la face, entre le dos du nez et le sourcil gauche pres de la racine du nez. Aussitôt après, les boutons deviennent de plus en plus nombreux, des vésicules se forment; les uns et les autres se répandent les jours suivants sur la partie gauche du front et du nez. Ne se sent pas malade et n'a aucune douleur. N'est pas incommodée par l'oeil. Admise à l'hôpital de 14 janvier; offre alors à la vue un très beau tableau d'éruption zostérienne sur le territoire des deux branches supérieures du trijumeau; (voir les photographies). Il y a lieu de signaler la présence de vésicules au bout du nez et à la lèvre supérieure. Sur le palais, près de

la ligne médiane, deux plaques muqueuses typiques. (Il se peut que ce cas puisse être considéré comme une éruption zostérienne n'intéressant que la première branche du trijumeau si l'on suppose un développement anormal exagéré du nerf naso-ciliaire.) Les paupières étaient très modérément enflées. Deux glandes lymphatiques d'un volume grossi et légèrement sensibles étaient palpables sur le côté gauche du cou, derrière l'angle maxillaire. Les yeux ne présentaient rien de pathologique. L'acuité visuelle était de 5/5 pour chacun des yeux, sans correction. La température atteignit son maximum le 16 janvier et fut ce jour-là de 38,3°, puis elle tomba progressivement et le 19 janvier elle était redevenue normale. Pas de nouvelles vésicules après le 16 janvier. Le 20 janvier on remarqua sur la cornée de l'oeil gauche, vers la périphérie, deux petites infiltrations assez superficielles. L'épitélium était indemne. L'oeil était tout à fait clair. Aucun signe d'irritation de l'iris. La pression intraoculaire était normale. Pendant tout le cours de sa maladie la petite fille s'est sentie tout à fait bien portante et n'a ressenti aucune douleur. A sa sortie de l'hôpital, le 23 janvier, elle n'avait plus que quelques croûtes au front. Une semaine plus tard sa peau ne présentait en somme rien d'anormal; il ne subsistait que quelques cicatrices insignifiantes. Ses yeux étaient clairs, sans traces d'irritation. L'acuité visuelle était de 5/5 pour chacun des yeux, sans correction. On pouvait encore apercevoir un petit point trouble sur la cornée de l'oeil gauche.

Ce qui est commun aux cas que je viens de relater, c'est l'évolution particulièrement paisible et brève de la maladie. L'éruption cutanée était bien développée, mais n'a pas occasionné de vraies gênes locales. Les névralgies étaient complètement absentes. Des complications oculaires ne se sont produits que dans le dernier des cas décrits plus haut et encore dans une mesure si insignifiante qu'on ne s'en serait certainement pas aperçu si, craignant que l'oeil ne pût rester indemne, on ne l'avait, dès le début, spécialement examiné très minutieusement. En effet, déjà Hutchinson avait signalé que, quand le bout du nez était attaqué par l'éruption zostérienne, il était très probable que l'oeil l'était également. C'est là une vieille règle clinique dont la véracite se trouve souvent confirmée.

Summary

To get an idea of the incidence of zoster ophthalmicus in children, the author studied the hospital records of 291 cases of zoster ophthalmicus. The distribution in the different age-groups

was graphically represented. The curve thus constructed showed, firstly that zoster ophthalmicus is commonest among old people, secondly that it is very rare in children. Among the 291 cases there were only two patients under ten years of age. These two cases in which the author personally followed-up the evolution of the disease, are reported at greater length.

The characteristical clinical symptoms produced by zoster, in particular those marking the type localized to the face, are described. In view of the fact that zoster in children differs in several respects from that observed in adults, the author takes up the question whether this applies also to zoster ophthalmicus in children.

Résumé

Dans le but de se faire une conception plus exacte de la fréquence du zona ophtalmique chez l'enfant, l'auteur a compulsé un nombre considérable de fiches d'observations concernant les cas de zona ophtalmique, soit 291 cas. Il a établi une courbe montrant la répartition de ces cas suivant l'âge des malades. Il ressort de cette courbe que le zona ophtalmique est surtout une maladie s'attaquant aux personnes agées tandis qu'elle est très rare chez l'enfant. Parmi ces 291 cas, il n'y en avait que deux qui concernaient des malades âgés de moins de 10 ans, et l'auteur, qui a eu l'avantage de pouvoir observer ces deux cas pendant toute la durée de la maladie, les décrit en détail.

En outre l'auteur résume les principales manifestations cliniques de l'infection zostérienne et souligne certains traits typiques caractérisant sa localisation à la face. Enfin, le zona chez l'enfant différant, comme on le sait, sous divers rapports du zona chez l'adulte, l'auteur soulève la question de savoir dans quelle mesure cette différence subsiste quand il s'agit du zona ophtalmique.

Zusammenfassung

Um einen Überblick über die Häufigkeit des Zoster ophthalmicus bei Kindern zu bekommen, har Verf. die Krankengeschichten von 291 Fällen von Zoster ophthalmicus eingehend studiert.

Die Verteilung innerhalb der verschiedenen Altersgruppen wurde graphisch dargestellt. Die Kurve veranschaulicht einerseits, dass der Zoster ophthalmicus in erster Reihe eine Krankheit des Alters ist, andererseits, dass er bei Kindern äusserst selten vorkommt. Unter den 291 Fällen waren nur zwei Patienten, die jünger als zehn Jahre waren. Diese beiden Fälle, in denen Verf. den ganzen Verlauf der Krankheit persönlich verfolgen konnte, werden ausführlich beschrieben.

Es wird ein kurzer Überblick über die charakteristischen klinischen Symptome des Zoster im allgemeinen gegeben, wobei die Merkmale, welche die im Gesicht lokalisierte Art dieser Krankheit kennzeichnen, ausführlicher beschreiben werden. Die bekannte Tatsache, dass sich der bei Kindern beobachtete Zoster in mancher Hinsicht von dem, der bei Erwachsenen vorkommt, unterscheidet, veranlasste den Verf., die Frage zu behandeln, ob sich dieser Unterschied auch beim Zoster ophthalmicus geltend macht.

Resumen

Con objeto de obtener una concepción más exacta de la frecuencia del zona oftálmico de la infancia, el autor ha examinado un número considerable de fichas de observación respecto a los casos de dicha afección, es decir: 291 casos. Ha compuesto una curva gráfica mostrando la repartición de estos casos según la edad de los enfermos. Se desprende de esta curva que el zona oftálmico es una enfermedad que especialmente ataca a personas de edad, mientras que es muy raro en la infancia. Entre estos 291 casos no había más que dos que correspondieran a enfermos de menos de 10 años, y el autor, que ha tenido la ventaja de poder observar estos dos casos durante toda la duración de la enfermedad, los describe detalladamente.

Entre otras cosas el autor resume las principales manifestaciones clínicas de la infección de zoster y recalca ciertos rasgos típicos caracterizando su localización en la cara. Finalmente el zona de la infancia difiere, como se sabe, en diversos aspectos, del de adultos. El autor plantea la cuestión de saber en qué grado esta diferencia subsiste cuando se trata del zona oftálmico.

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FROM THE MEDICAL DEPARTMENT OF THE CHILDREN'S HOSPITAL, GOTHENBURG, SWEDEN.

A Report on Combined Sulfonamides-Penicillin Treatment of Acute Purulent Meningitis and a Follow-Up Study

by

T. TORSTENSON

The prognosis for acute purulent meningitis has long been very bad. For some types mortality has been 95—100 %. Sulfonamides have brought some improvement, however. In 1945 E. Jacobson reported on the cases of pneumococcic and haemophilus influenzae-meningitis treated with sulfonamides at the Children's Hospital, Gothenburg, during 1938—44. Owing to considerably larger doses of sulfonamides a certain reduction in mortality could be shown. This was especially the case for meningitis caused by B. haemophil. infl. Many others have had the same experience.

Table 1 shows that 19 out of 29 belonging to Jacobsson's series died. Practically all of the survivors belonged to the group aged over 1 year: only 4 out of 13 died. There were 16 infants, of whom 15 died.

Table 1.

I. 1938—44 II. 1945—48	Under 1 Year		Over 1 Year		Total	
	Cases	Died	Cases	Died	Cases	Died
Pneumococcic I.....	9	8	3	2	12	10
II.....	8	0	3	0	11	0
B. Haem. Infl. I.....	7	7	10	2	17	9
II.....	7	1	7	0	14	1
Total I.....	16	15	13	4	29	19
II.....	15	1	10	0	25	1

Since penicillin has been available in sufficient quantities results have been much better. Table 1 shows the mortality for the same types of meningitis treated during 1945—48 at the Children's Hospital, Gothenburg. Of 25 cases only 1 died (an infant). Moreover, 9 of the 11 cases of pneumococcic meningitis were less than 2 years of age, as were 10 of the 14 caused by B. haemophilus influenzae.

Table 2 shows all cases of acute purulent meningitis treated during 1945—47 except the meningococcic cases. These are treated at the Hospital for Contagious Diseases. (The cases of 1948 are excluded, as they have not yet been the object of any follow-up study.)

Table 2.

Bacteria	Under 1 Year		Over 1 Year		Total	
	Cases	Died	Cases	Died	Cases	Died
Pneumococci	7	0	2	0	9	0
B. Haemoph. Infl.	6	1	4	0	10	1
Uncertain	6	2	5	0	11	2
Total	19	3	11	0	30	3

Besides the types of meningitis just mentioned there were 11 cases in which the bacteria, in spite of purulent cerebrospinal liquor, could not be identified either by dyeing or by cultures (undoubtedly some of them could have been meningococcic). Of these 6 were infants, 2 of whom died. Thus among 30 cases of acute purulent meningitis 19 were infants, of whom 3 died. Eleven were children over 1 year of age, among whom there were no deaths.

Treatment

Since 1945 we have used both sulfonamides and penicillin. The sulfonamide generally used is Sulfadimin (Astra) 2-sulfanilamido-4-methylpyrimidin. It has been given only orally. The principle has been to make the dose sufficiently large to maintain the optimum concentration of sulfonamide in the cerebro-

spinal liquor (according to Frisk this is 8—10 mgm % for Sulfadimin). For this purpose we have often used four times the initial dose usually given for pneumonia (it has usually been 0.1 gm or more per kg body weight). In this manner the patient has received a large quantity of sulfonamides (1 patient received 370 gm). The concentration in the cerebrospinal liquor has been checked at every lumbar puncture.

Penicillin has been given both intramuscularly and intraspinally. Intramuscularly we have never given less than 100 000 units a day and initially often 200 000—300 000 units or even more. It has always been divided into eight doses. Intraspinally we have usually given 10 000 units at a time every 24 hours but the first few days often 20 000 or sometimes 25 000—35 000 units, dissolved in 8—10 ml saline solution. In severe cases we have sometimes given the dose every 12 hours during the first few days.

At the endolumbar puncture, cerebrospinal liquor has been drawn, preferably as much as possible (drainage). Each time the cell and bacteria content of the liquor has been examined, as has the concentration of sulfonamides.

It has been a delicate problem to know when the treatment could be stopped. If it is done too early, severe relapses often occur. When the clinical symptoms of meningitis have disappeared, the treatment is gradually discontinued. But there must be no fever. The patient must be in a very much improved general condition, with good appetite, etc. There must be an obvious diminution in the number of cells in the cerebrospinal liquor as well as repeated negative cultures.

First the intraspinal injections of penicillin have been given more infrequently — every forty eighth hour, seventy second hour, and so on. If relapse has followed they have been given more frequently again. Then the intramuscular injections have been discontinued. Not until the sedimentation rate shows permanently decreasing values down to the normal state is sulfonamide also taken away. The cerebrospinal liquor is examined bacteriologically and microscopically several times after the intraspinal injections have been discontinued.

Comments

There are some comments to be made. The decreased mortality that others have reported from treatment with sulfonamides does not include the youngest patients. B. haemophilus influenzae is generally not responsive to penicillin (except some strains). However, the present material points to the conclusion that there is a greater effect when sulfonamides and penicillin are used together against these bacteria. There are cases here in which the resistance test showed that the bacterium in question was only slightly susceptible to sulfonamides and was resistant to penicillin, yet the patient recovered with the combined treatment.

The deaths can give some information. Thus the one death among the haemophilus influenzae cases shows the risk of withdrawing the treatment too early.

No. 754/45 A boy 8 months of age. After a week with catarrhal symptoms convulsions suddenly set in. Purulent meningitis caused by B. haemoph. infl. was detected. After intensive treatment with Sulfadimin and penicillin for 12 days, penicillin was withdrawn. The clinical symptoms had then disappeared, several cultures were negative, and the number of cells had diminished considerably. But there was still fever and the sedimentation rate was high. In three days there came a deterioration and culture was positive again. In spite of large doses of sulfonamides the patient died 25 days after the first signs of meningitis.

This was one of our first cases. Later we would have delayed the withdrawal of treatment till there was no fever and a more normal sedimentation rate. Perhaps the case also suggests the better effect of the combined treatment.

Among the cases without bacteriological diagnosis there were two deaths. Both involved infants (Nos. 698/47 and 1139/47) who were comatose when they were brought to the hospital. They died within 36 hours.

Complications

The complications have generally not been serious. In our first 3 cases with combined sulfonamides-penicillin treatment

there appeared thrombopenia and disseminated efflorescences resembling erythema multiforme with petechiae. (The cases have been reported by K. Holmdahl.) Some other cases also showed transient thrombopenia with petechial efflorescenses.

Signs of slight renal injuries with microscopical haematuria have been seen in several cases. These generally passed off without necessitating suspension of the treatment. Only 1 case showed important signs of renal injury.

No. 811/46. A boy 1 1/2 years of age. Albuminuria, haematuria, cylindruria, and an increase in the non-protein nitrogenous elements in the blood set in. These decreased when double doses of alkali were given. One month later both penicillin and sulfonamides were withdrawn. The patient was in good condition. A week later, however, symptoms of meningitis reappeared, including a positive culture, and treatment had to be begun again. Five weeks later there came another increase in the N. P. N. It disappeared when all treatment ceased. The meningitis was now cured. When the patient left the hospital three months after admission he had no signs of renal injury.

Often the patients were hypertensive and irritated after the endolumbar injections. In general, however, they stood them astonishingly well.

Convulsions are, of course, frequent, but they are seldom of such a kind as to cause one to consider stopping the treatment. That has happened in only 2 cases. Both were comatose when they were brought to the hospital. They were:

No. 1764/47. A girl 3 months of age. The bacterium unknown. There were convulsions and paresis. Within some days, when the patient was better — though the cells in the spinal fluid still exceded 1000 — she had several convulsions in direct consequence of the injections of penicillin. Later hydrocephalus and other signs of cerebral injury appeared. The child died 4 months later.

No. 2072/47. A girl 7 1/2 months of age. The meningitis was caused by B. haemophilus infl. The child was in very bad condition when she came in for treatment. She was much better after a week, with a greatly diminished number of cells in the spinal fluid. In the first week six injections were given but in the second only two. After the sixth injection the patient was hypertensive but there were no further complications. Nothing remarkable happened after the next two injections. After the ninth, however, the patient was hypertensive again; convulsions and then hyperpyrexia with coma followed. At three later lumbar punctures

without injections of penicillin the number of cells found was very small. In this case, too, there were lasting signs of serious cerebral injury, but no hydrocephalus.

Perhaps the largeness of the intraspinal dose is of importance. In these 2 cases 20 000 units were given at every injection.

A Follow-Up Study

The immediate result, with 27 survivors out of 30 cases, is promising. But in order to estimate the real value of the treatment one must make a follow-up study of the subsequent health of each patient. Such a study has been made. It has consisted in part of a somatic and in part of a psychiatric examination with determination of the intelligence quotient (I. Q.). The psychiatric examination was made by Dr. E. Regnér and Miss K. Thorén, the Social Worker at the Child Guidance Clinic.

For the majority of the patients the observation time has covered a period of from one to three and one-half years. For 3 of them it was nine to ten months but for one not more than six months. Six months may be enough for our purpose, since the period for the onset of complications after meningitis is said to be less than three to four months.

The patients were divided into the following groups:

1. cases without any sequelae,
2. cases with lasting psychasthenic symptoms,
3. cases with neurological defects or serious organic cerebral injuries, and
4. cases who died in the acute stage.

One of the patients has not come for examination but the parents have answered a questionnaire. The child was 5 months of age when she had meningitis and 2 1/2 years of age when the parents answered. It appears from their answer that she has developed normally, without any obvious behaviour disturbances.

The Group 3 cases have not undergone any psychiatric examination.

In Table 3 the distribution of the cases among the groups just mentioned is seen.

Table 3.

Bacteria	Group 1	Group 2	Group 3	Total
Pneumococci	4	2	3	9
B. Haemoph. Infl.	3	5	1	9
Uncertain	3	5	1	9
Total	10	12	5	27

Thus 10 cases have not had any sequelae.

Symptoms represented among the 12 cases in Group 2 are: naughtiness, rashness, irritability, obstinacy, timidity, restlessness, headache and decreased ability to learn and concentrate, and finally a low mental age (M. A.). Such diverse symptoms are susceptible of many interpretations. A serious illness, independent of its nature, involving a long period in hospital, can be sufficient explanation. A case in point is as follows.

No. 1344/46. A girl 5 months of age on admission. She had nephrosis and a general infection of pneumococci with two distinct foci, in the peritoneum and the meninges. The general infection was stopped with penicillin (no sulfonamides were used here). But the patient was constantly in low health because of her nephrosis with large oedema and many recurrences of infection, often in the form of erysipelas. She died after two years. She had been in the hospital most of the time. Her psychomotor development was delayed and she had a low M. A.

In Table 4 the cases are divided into two groups

A. those with M. A.'s equal to or more advanced than their chronological age (C. A.), and

B. those with M. A.'s below their C. A.'s.

Among the 8 cases in Group B the difference between the M. A. and the C. A. is not more than two months for 4 and 3 months for 1 of them. Thus one may say that 18 were in good mental health after meningitis. To these may be added the case that was not tested: i. e. a total of 19 cases.

In the other 3 cases in Group B the difference between the M. A. and the C. A. were twelve, ten, and six months.

Table 4.

		Group 1	Group 2	Total	
	Group A.				
M.A. ≧ C.A.	Pneumococci	3	–	3	13
	B. Haemoph. Infl.	3	2	5	
	Uncertain	2	3	5	
	Group B.				
M.A. < C.A.	Pneumococci	1	2	3	8
	B. Haemoph. Infl.	–	3	3	
	Uncertain	–	2	2	

In Group 3 (see Table 3) there are 5 cases. One of them has a lasting neurological defect.

No. 1934/46. The patient was 5 1/2 months of age when he fell ill with meningitis caused by pneumococci. When he left the hospital one and one-half months later there was still paresis. It disappeared soon. But more than two years later he still cannot talk. The cause is deafness (ascertained by an earspecialist at 1 year of age). He could walk at 16 months of age and he is overexcited.

Common to the other 4 is the fact that one could tell at an early stage that the prognosis was bad. One was mentioned before — the case with hydrocephalus that died five months after the beginning of the meningitis. The others did not have hydrocephalus but all of them show extreme dullness, with retarded psychomotor development. One of them has petit mal and another athetotic movements. All of them were less than 1 year old when the meningitis began (3, 6, 7 1/2, and 7 1/2 months old, respectively).

Thus the follow-up study shows that of the survivors, 5 have lasting, serious cerebral injuries (1 has since died); 3 have a markedly delayed psychomotor development together with psychasthenic symptoms (one of them has died of another disease); and 19 have no or merely unimportant sequelae.

The following factors can be considered important to the

prognosis: age, the lapse of time before treatment begins, the patient's condition at the start of the treatment, the type of bacteria, the number of cells in the spinal fluid and the number of intraspinal injections. These factors are illustrated by the following tables.

The deaths appeared among the infants, and Table 5 shows that the survivors among the infants had the most serious injuries.

Table 5.

Group	3—6 Months	6—8 Months	8—10 Months	10—12 Months	1—2 Years	Over 2 Years
1.	3	1	1	1	2	2
2.	1	1	2	1	2	5
3.	2	1	2	–	–	–
4.	2	1	–	–	–	–

It is of course of great importance that the patients be attended as soon as possible. It is not possible to demonstrate this from the present material, due to the fact that it is very hard to know exactly when the meningitis really started.

Table 6 shows the states of the cases when they came to the hospital (each case is shown once only, in the column for its most serious symptom).

Table 6.

Symptom	Group 1	Group 2	Group 3	Group 4
Coma } Somnolence }	3	3	3	3
Paresis	–	1	2	–
Convulsions	3	1	–	–
Vomiting	3	–	–	–
Stiff Neck	1	4	–	–
Miscellaneous: Headache, etc., Pneumonia, etc.	–	3	–	–

It can be seen here that nearly 2/3 of the cases had very serious symptoms, including all cases in Groups 3 and 4. The ones that originally had slight symptoms have recovered without any or with merely unimportant sequelae. The not unexpected conclusion will be that serious symptoms in the beginning are unfavourable for the prognosis. But evidently they are not invariably unfavourable, for many of the cases in Groups 1 and 2 had the most serious symptoms too.

A close examination of Table 4 might possibly reveal different prognoses for the different types of meningitis. For example, it is perhaps significant that the 2 cases in Group 2 caused by pneumococci were those with the greatest difference between the M. A. and the C. A.: 12 and 10 months, respectively. In the case with a six month difference the bacterium was not identified.

Thus 8 out of 10 cases caused by B. haemophilus infl. and 7 out of 11 unknown but only 4 out of 9 pneumococcic cases have regained a satisfactory state of health.

However, it must be pointed out that home environment and hereditary factors were undoubtedly of importance in the case with the 12 month difference. The mother of the child with the six month difference was feeble-minded and the father a deaf-mute. The case with the 10 month difference was the child with nephrosis who spent a long time in hospital.

In Table 7 we see how the cases in the various groups are distributed with regard to the number of cells in the spinal fluid

Table 7.

Group	1.	2.	3.	4.
< 100	1	1	–	–
100— 500	–	4	2	1
500— 1 000	–	1	–	–
1 000— 5 000	3	4	1	1
5 000—10 000	4	–	–	–
10 000—20 000	2	2	2	1

Table 8.

Group	1.	2.	3.	4.
500— 1 000	2	–	–	–
1 000— 2 000	1	4	–	–
2 000— 4 000	2	4	1	–
4 000— 6 000	–	–	1	–
6 000—10 000	3	–	1	–
10 000—15 000	–	2	1	1
15 000—20 000	2	–	1	1
over 20 000	–	2	–	1

at the first lumbar puncture and in Table 8 with regard to the highest number found.

We see in Table 8 that all cases in Groups 3 and 4 had many cells. There is a similar trend in Table 7, but it is less pronounced. Furthermore, several cases in the other groups also had a large number. Perhaps one may venture to express the situation in the following manner: the idea that the number of cells is an indication of the seriousness of the meningitis is not contradicted. However, it seems that one cannot make the prognosis on the basis of the number of cells.

Table 9 shows the number of intraspinal injections given.

Table 9.

	2—10	11—15	16—20	21—30	31—50	>50
Group 1...	1	1	2	5	1	–
» 2...	2	4	–	3	3	–
» 3...	1	–	2	–	–	1
» 4...	2	–	–	1	–	–

One sees that several cases in Groups 1 and 2 had many injections. The conclusion is that one should not give up hope if many injections must be given. Or, in other words, the risks of giving endolumbar injections of penicillin cannot be very great. For the present one should not hesitate to use them.

Summary

Combined sulfonamides-penicillin treatment of acute purulent meningitis has given promising results. The sulfonamides have been given orally in large doses and the penicillin intramuscularly (100 000—300 000 units a day) and intraspinally (10 000—20 000 units once or twice a day). Twenty seven patients out of 30 survived. Of 19 infants only 3 died. A follow-up study shows that 19 of 27 were cured without any or with merely unimportant sequelae. Five patients still show signs of cerebral injuries and 3 markedly delayed psychomotor development and psychasthenic

symptoms. Furthermore, this study shows that: 1. the survivors among the infants had the most serious injuries, 2. serious symptoms in the beginning are not invariably unfavourable; 3. the prognosis for the peumococcic type of meningitis is perhaps less favourable; 4. the prognosis cannot be based on the number of cells in the cerebrospinal fluid; and 5. the risk involved in giving endolumbar injections of penicillin cannot be great.

Résumé

Un traitement combiné: sulphonamide-pénicilline, pour la méningite purulente aiguë a donné un résultat qui donne des espérances. La sulphonamide a été administrée per os, a grandes doses, la pénicilline par voie intra-musculaires (100 000—300 000 unités par jour) et intra-spinales (10 000—20 000 unités, une ou deux fois par jour). Vingt-sept patients sur trente, ont survécu. Sur dix-neuf enfants, trois seulement sont morts. Une étude suivie montre que dix-neuf sur vingt-sept étaient guéris et ne présentaient aucune, ou seulement d'insignifiantes séquelles. Cinq patients avaient des signes durables de lésions cérébrales et trois, un développement du psychomoteur visiblement retardé, ainsi que des symptômes de psychasténie. De plus, elle montre que 1. les survivants parmi les enfants de moins d'un an avaient les lésions les plus graves, 2. de graves symptômes au début n'est pas invariablement défavorable, 3. c'est peut-être un prognose moins favorable pour la méningite à pneumocoques, 4. le nombre de cellules dans le liquide céphalo-rachidien ne peut pas affirmer le prognose et 5. le risque de donner des injections intralombaires de pénicilline ne peut être grand.

Zusammenfassung

Eine kombinierte Sulphonamid-Penicillin-Behandlung der akuten eitrigen Meningitis hat hoffnungsvolle Resultate ergeben. Die Sulphonamide wurden per os in grossen Dosen gegeben, das Penicillin intramuskulär (100 000—300 000 Einh. täglich) und intraspinal (10 000—20 000 Einh. ein- oder zweimal täglich). 27 Patienten von 30 blieben am Leben. Von 19 Kindern unter einem Jahr

starben nur 3. Eine nachfolgende Untersuchung zeigte, dass 19 von 27 ohne irgendwelche oder mit nur unbedeutenden Folgeerscheinungen geheilt waren. 5 Patienten haben Anzeichen zerebraler Schäden, und 3 solche verzögerter psychomotorischer Entwicklung und psychoasthenische Symtome davongetragen. Ausserdem zeigte sich dass: 1. die Überlebenden unter den Kindern unter einem Jahr die schwersten Erscheinungen gehabt hatten, 2. schwere Symtome im Beginn nicht unveränderlich ungünstig sind, 3. die Prognose für den Pneumokokken-Typ der Meningitis vielleicht weniger günstig ist, 4. die Zellenanzahl in der Zerebrospinalflüssigkeit die Prognose nicht beeinflussen kann, 5. das Risiko bei der intralumbalen Injektion von Penicillin nicht gross sein kann.

Resumen

Un tratamiento combinado con sulfamidas-penicilina de casos de meningitis aguda purulenta, ha dado resultados prometedores. Las sulfamidas fueron administradas por vía oral en grandes dosis, la penicilina por vías intramuscular (100 000—300 000 unidades diarias) y endoespinal (10 000—20 000 unidades una o dos veces al día). De treinta pacientes sobrevivieron veintisiete. De diecinueve niños fallecieron solamente tres. Un estudio de la historia clínica muestra que de veintisiete casos, diecinueve fueron curados sin ninguna o con muy ligera y no importante complicación. Cinco pacientes han quedado con síntomas de lesiones cerebrales y tres con un marcado retraso en el desarrollo psicomotor y síntomas psicasténicas. Además de esto el estudio demuestra que: 1. Entre los supervivientes son los infantes de menos de un año los más seriamente dañados. 2. Síntomas serios al principio no son invariablemente desfavorables. 3. El pronóstico es quizá menos favorable para el tipo pneumocócico de meningitis. 4. El número de células en el líquido cerebro-espinal no puede determinar el pronóstico. 5. El riesgo de administrar inyecciones de penicilina por vía endolumbar no puede ser grande.

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FROM THE CHILDREN'S DEPARTMENT OF RIGSHOSPITALET, COPENHAGEN.
CHIEF: PROF. P. PLUM, M. D.

Atresia of the Oesophagus

Reconstruction of the Intrathoracic Oesophageal Continuity by the Transpleural Approach in Two Instances[1]

by

TYGE CL. GERTZ

Owing to the rapid progress within the field of thoracic surgery in the course of the last decade, surgery is now applicable with success in a number of congenital malformations which formerly were considered outside the range of surgical treatment. One of the conditions in which striking results have been attained is congenital atresia of the oesophagus, a malformation which untreated is bound to lead do death in the course of the first or second week of life. In the first cases who survived, the operation was performed in several stages, ending in antethoracic oesophagoplasty, but in 1941 CAMERON HAIGHT succeeded in making a primary anastomosis between the two oesophageal segments. It goes without saying that this is the ideal form of operation. It is completed in one stage and the result is a condition completely normal or as close to normal as at all possible.

There are several types of atresia of the oesophagus. In exceptional cases the organ may be absent, but in the majority of cases it is divided into two segments, both ending in a blind pouch unless one or both communicate with the trachea by a fistula. The most common condition, found in about 90 per cent, is that in which the upper segment ends in a blind pouch and the lower one enters the trachea near or at the level of the bifurcation. Fortunately, this is the type which is most amenable to primary an-

[1] Read before the Pædiatric Society on April 27, 1949.

astomosis. — Among 42 cases operated on since 1939, HAIGHT was able to use primary anastomosis in 32, and among the instances of the most common variety, the operation was successful in 83,3 per cent. LADD & SWENSON, who also have wide experience, were, however, unable to make a primary anastomosis in more than 32 of 76 instances. — It is not surprising that the mortality attending these operations is still rather high. In 1944 HAIGHT reported 6 survivors among 16 subjected to intrathoracic oesophageal restoration. LADD & SWENSON, in 1947, reported an aggregate mortality of 60 per cent, and out of 32 submitted to primary anastomosis 18 died. Since then SWENSON has, however, reported considerably improved results.

No doubt the incidence of atresia of the oesophagus is much higher than ordinarily assumed. Comparing the number of cases with the number of births in a relatively limited area, HAIGHT found an incidence of 1 in 2196, in other words almost as high as that of harelip and cleft palate. In general it is not believed that the incidence is so high, presumably because a large number of the intants die before the diagnosis is made. Premature birth is a frequent complication and this is in itself attended with a high mortality during the first days of life. The condition does not appear to co-exist with particular frequency with other malformations, perhaps with the exception of cardiovascular anomalies.

If only the condition is borne in mind, the diagnosis ought not to be difficult. It gives rise to characteristic symptoms, rhonchi resulting from bronchial secretion and salivation, right from birth, attacks of choking and cyanosis upon attempts to swallow. Passing of a soft catheter down the oesophagus gives the diagnosis. If it meets obstruction 10—12 cm from the lips, atresia is present. Percussion reveals the existence of air in the stomach, an indication of a fistulous communication between the trachea and the lower segment. More definite evidence is obtainable by x-ray. The opaque medium poured down through the catheter will reveal the upper blind pouch and, in addition, possibly a tracheo-oesophageal fistula in this segment. Gas in the stomach and intestine is visualized on a plain film of the abdomen. In the writer's

opinion it is, however, wise to think twice before resorting to examination with contrast medium, as this involves the risk of overflow, filling the bronchi. As will be apparent from the following pages, this diagnostic measure can easily be dispensed with.

As yet the great majority of reports of successful operations have come from America. The largest series have been mentioned above. In Scandinavia, SANDBLOM was the first to succeed in the operation of primary anastomosis in November 1947. During the first months of 1948 he performed two additional operations, both of which were successful. He has not reported the mortality. In Denmark the first attempt at this operation was made by HUSFELDT in early 1947, but the infant died shortly after the operation. This case was mentioned by GERTZ in a paper read before the Surgical Society in 1947. Since then the operation has been performed eight times at Rigshospitalet, twice in the Department of Thoracic Surgery and six times in Surgical Department D. None of the infants survived the operation for more than three days, and as far as I can gather from the case records, the anastomosis was satisfactory in only 3. Since December 1948 I have had occasion to operate upon 4 cases. One is still alive five months later, and one died on the sixth postoperative day from a cardiac malformation.

The first 2 cases were operated upon by the almost universally recommended right-sided extrapleural approach. After resection of the third to sixth ribs posteriorly on the right side, the pleura was cautiously pushed forward from the chest wall and mediastinum, thus exposing the oesophagus. This is the method used in all the cases which have been operated upon in Denmark and in SANDBLOM's cases. In both instances the two segments of the oesophagus could be isolated and the tracheo-oesophageal fistula closed, but it was impossible to approximate the segments sufficiently to reconstruct the oesophageal continuity. One of the patients died on the second post-operative day and the other one was operated upon on the following day by HUSFELDT. Through a leftsided thoracotomy he mobilized the stomach, pulling it into the thorax where it was anastomosed to the upper cul-de-sac, i. e. the procedure used in oesophageal carcinoma. The intervention

was technically successful but it proved too much for the patient, who died a few hours later.

Faced with the third case, I decided upon the transpleural approach in spite of the fact that most authors warn against transpleural operations at this age. My reasons were as follows. In the first place, it must be presumed to give a much wider access. The extrapleural operation is cumbersome and time-consuming and does not give a particularly generous exposure. In addition, it is difficult to avoid perforating the extremely thin pleura. Lastly, I felt that it was advantageous to put the diaphragm out of action temporarily, as I had noticed that the movements of this organ exerted considerable traction on the lower segment during the inspiratory phase of respiration. On the one hand this interfered with the attempts at constructing an anastomosis, while on the other it must be presumed to have an unfavourable influence on the latter during the period of healing.

The third case was a baby girl aged 2 $^1/_2$ days transferred from a provincial town. Her birth weight was 2 700 g and she had exhibited signs of atresia of the oesophagus right from birth. She was small and thin, slightly jaundiced and showed reduced turgor of the skin. A catheter advanced down the oesophagus was arrested 11 cm from the lips, and percussion revealed a tympanitic sound over the abdomen. Without wasting any time on x-ray examination, the patient was operated on under intratracheal anaesthesia after having received a blood transfusion.

The chest was opened with an incision splitting the fifth intercostal space. In order to prevent shock, local anaesthesia was administered to the vagus nerve, and the right phrenic nerve was clamped with a Péan's forceps in order to arrest the movements of the diaphragm. An excellent exposure was obtained, and the two segments of the oesophagus were discernible through the thin mediastinal pleura. After division of the azygos vein and the pleura, both segments of the oesophagus could easily be freed. As had been expected, the upper segment ended in a blind pouch, whereas the lower one entered the trachea immediately above the bifurcation. Posteriorly there was a kind of bridge between the two segments, presumably made up of strands of the muscular

coat. This bridge was left intact while the tracheo-oesophageal fistula was divided close to the trachea and the opening in the latter closed with a continuous silk suture. Thereupon a small incision was made into the bottom of the upper segment and the mucous membrane on the posterior wall of both segments united with a number of fine interrupted silk sutures. This could be effected without causing tension. A No. 10 F catheter was passed down into the stomach and over this catheter the anterior wall was closed with fine interrupted silk sutures in two layers, the outer one only involving the muscular coat. The catheter was removed, the mediastinal pleura closed with interrupted catgut sutures, two of which included the oesophagus on either side of the anastomosis for the purpose of further anchoring. After a thin drain had been inserted through the sixth intercostal space, the lung was re-expanded and the chest wall closed. On the whole the postoperative course was uneventful. On the second postoperative day the temperature rose to 40.4° C, probably because of dehydration, but apart from that the temperature did not exceed 38° C. There were not at any time signs of pneumonia, even on the x-ray films (Fig. 1). She received prophylactic penicillin during the first postoperative days. Thirty six hours after the operation she was fed, first with a glucose solution, 10 g at a time, and as this could be swallowed without difficulty, she was given human milk in increasing doses. On the third day she had reached a total amount of almost 300 g in 24 hours. The pleural drain, which had yielded practically nothing, was removed on the seventh day. Ample salivation persisted for a long time after the operation. This was particularly embarrassing at the beginning of each feeding, and for a time the mucus was aspirated before the feedings. When she was discharged six weeks after the operation this was rapidly subsiding and aspiration had not been necessary for a long time. X-ray showed a rather marked constriction at the site of the anastomosis, but as she was able to take as much as 180 g from her mother, this stricture was apparently of no functional significance. At the time of writing the patient is almost 5 months of age and doing well.

Unfortunately the fourth case did not run so favourable a

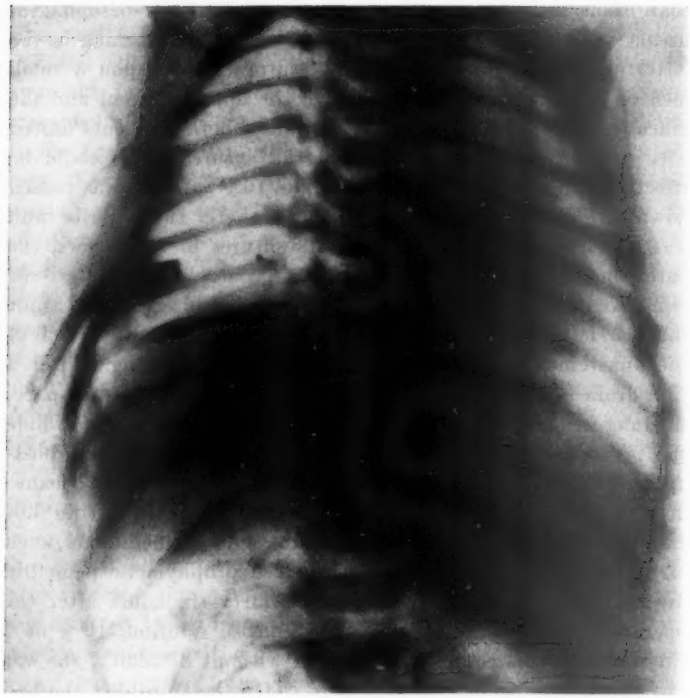

Fig. 1.

course, although it looked promising at the outset. The patient was a boy aged 4 days who was born at a provincial hospital and transferred to the Department by ambulance plane after the diagnosis was made by x-ray. In the course of this examination so much opaque medium was used that it overflowed, filling the bronchi even as far as the fine bronchioles. The boys' birth weight was 2 550 g, but he had lost about 400 g. On arrival he was therefore somewhat dehydrated, but after he had been warmed up and had received a blood transfusion the operation was started, 2 $^1/_2$ hours after admission. In all essentials the procedure was like the one described above and I shall therefore not dwell on the

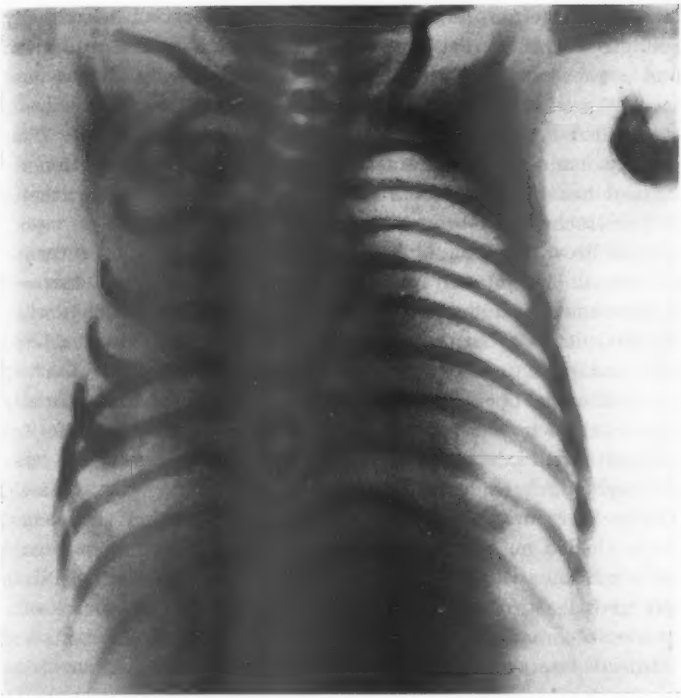

Fig. 2.

details. In this instance too the transpleural approach proved satisfactory. The two segments of the oesophagus were about 1 cm apart. Because of the experience from the previous case I began uniting the posterior wall of the two segments with a number of interrupted silk sutures involving the muscular coat before I incised the tracheo-oesophageal fistula. In this way it was possible to approximate the two segments without stretching them, and the operation was completed in the same way as the first one.

The baby did well during the operation and during the first hours after. He received first a transfusion of whole blood and

later one of serum, but 12 hours after the operation he suddenly collapsed, turning greyish pale and showing cessation of respiration and a poor cardiac action. I happened to pass by and at once started artificial respiration. During this manoeuvre the heart stopped and the child was given adrenalin intracardially. This quickly made the cardiac action normal but the respiration remained heaving and laboured. Aspiration with a thin catheter in the trachea and bronchi yielded a certain amount of viscid, greyish brown secretion. Thereupon the respiration also returned to normal. During the following days aspiration was performed in the same way four—five times daily until the sixth day, when the patient appeared to be doing so well that this was considered unnecessary. An attempt was made at feeding the infant 36 hours after the operation. As, however, this caused him difficulty and resulted in marked cyanosis it was abandoned and he was instead given human milk in increasing doses through a thin catheter which could easily be passed down into the stomach. The temperature remained normal all the time and the pleural drain yielded no secretion. Just as we were beginning to regard his condition with optimism, he suddenly collapsed on the sixth day and death occurred in marked cyanosis in the course of a quarter of an hour in spite of the administration of stimulants and artificial respiration. Immediately after death aspiration of the trachea and bronchi was attempted, but yielded nothing.

Postmortem examination failed to reveal any evidence of inflammation in the operative field. The pleura close to the anastomosis was not even coated and there was no air or effusion in the pleural cavity. The anastomosis was sufficient and ample. The lungs were somewhat hyperæmic, but there were no focal processes, and particularly no signs of pneumonia. A certain amount of mucus was found in the left bronchi, but none on the right side. Opening of the heart revealed an extremely large patent foramen ovale without valves. Moreover, the interauricular septum was thin and perforated in several places, so that it was actually a case of septal defect. No other malformations were demonstrable, but the findings are no doubt sufficient to explain the death as one due to heart failure, as was also indicated by the clinical picture.

The fatal outcome in this case can therefore not be put down to the operative procedure, and in my opinion the transpleural approach is preferable to the extrapleural approach, because of the following advantages: it is quicker and it affords a considerably more generous exposure, while the diaphragm can be put out of action, so that traction on the anastomosis is avoided both during the reconstruction and afterwards. Furthermore, the respiration is less apt to be affected after the operation. This last-mentioned fact is apparent *inter alia* from the finding of normal lungs in the writer's last case apart from a presumably terminal hyperæmia, whereas the postmortem examinations of all the patients who have undergone the extrapleural operation have disclosed atelectases and bronchopneumonia. These phenomena are also demonstrable by x-ray. Fig. 1 shows the lungs of my first patient submitted to transpleural operation on the first postoperative day, whereas Fig. 2 represents one of the extrapleural cases, also on the first postoperative day. In Fig. 1 the right lung field is clear and air-filled, whereas Fig. 2 shows a dense shadow.

Of course I dare not maintain that the outcome in my first 2 cases would have been better if I had used the transpleural route, but I think that this would have enabled me to construct the anastomosis, at least in the second one in which the distance between the two segments was short. In this very case the movements of the diaphragm proved a great obstacle. I am aware that I made a mistake in both cases in trying to free the tracheo-oesophageal fistula before I had tried fixing the two segments to each other. The lower segment has a tendency to retract when the connection to the trachea is divided, and it is then difficult to get hold of.

Unlike most authors I did not perform gastrostomy in any of my cases. This is done routinely by LADD & SWENSON on the first postoperative day, but by HAIGHT only if the sutures appear to be insufficient. I was not particularly inclined to expose my 2 patients to the extra strain of a gastrostomy and therefore tried to do without it. One of them could swallow as early as 36 hours after the operation. The other one did not have the

strength to swallow, but he could easily be fed with a tube. I am not sure whether the latter method is not actually preferable. It must be presumed to expose the fresh anastomosis to less strain than the act of swallowing.

Irrespective of the technique used, it is important to make the diagnosis as early as possible and with as simple means as possible. I am referring in particular to the use of contrast media, which I consider unsuitable. As emphasized above, the diagnosis should not cause difficulties if only the condition is borne in mind. — If atresia of the oesophagus should prove to be as common as HAIGHT's figures indicate, there is in my opinion reason to adopt a routine examination of all newborn infants for this condition just as they are now examined for cleft palate, atresia ani, and other malformations of the anogenital region. As the diagnosis can be made by merely trying to pass a soft catheter down the oesophagus, it should be practicable by any physician or midwife.

Summary

The writer presents 2 cases of atresia of the oesophagus with tracheo-oesophageal fistula. In both cases the oesophageal continuity was reconstructed by the transpleural approach. One of the patients is now 5 months of age and doing well, but the other died six days after the operation from a cardiac malformation. Autopsy showed a sufficient anastomosis. The advantages of the transpleural approach are emphasized, particularly the significance of being able to put the diaphragm out of action temporarily and a more free respiration with consequently reduced risk of pulmonary complications postoperatively. Gastrostomy did not prove necessary in either case.

Resumé

L'auteur nous présente deux cas d'atrésie de l'oesophage avec une fistule trachéo-oesophagienne, opérés tous les deux par voie transpleurale. L'un des malades a maintenant 5 mois et se porte bien, tandis que l'autre est décédé, six jours après l'opération, d'une malformation cardiaque. L'autopsie à montré une anastomose suffisante. Les avantages de la voie transpleurale sont

mis en évidence; particulièrement l'importance de la possibilité de mettre temporairement le diaphragme hors d'action, ce qui permet une respiration plus libre et réduit ainsi le danger d'une complication pulmonaire post-opératoire. On put éviter la gastrotomie dans les deux cas.

Zusammenfassung

Der Autor stellt 2 Fälle von Ösophagusatresie mit Tracheo-Ösophageal-Fistel vor. In beiden Fällen wurde die Kontinuität des Ösophagus durch transpleurale Annäherung hergestellt. Einer der Patienten ist jetzt 5 Monate alt und befindet sich wohl, der andere starb 6 Tage nach der Operation an einer Herzmissbildung. Die Autopsie ergab eine sufficiente Anastomose.

Der Vorteil der transpleuralen Annäherung besteht besonders in der Möglichkeit das Diaphragma zeitweise aus der Funktion zu setzen, in freierer Atmung und folglich geringerem Risiko für postoperative Lungenkomplikationen. Gastrostomie ist in solchen Fällen nicht notwendig.

Resumen

El autor nos presenta dos casos de atresia del esófago con una fístula traqueo-esofágica, operados los dos por vía transpleural. Uno de los enfermos tiene ahora 5 meses y sigue bien, mientras que el otro falleció seis días después de la operación, de una perturbación cardíaca. La autopsia muestra una anastomosis suficiente. Se ponen en evidencia las ventajas de la vía transpleural, particularmente la importancia de la posibilidad de dejar el diafragma fuera de acción temporalmente, lo cual permite una respiración más libre reduciendo así el peligro de una complicación pulmonar postoperatoria. La gastrotomía pudo evitarse en los dos casos.

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CHIEF: PROF. P. PLUM, M. D.

Intestinal Obstruction in the Newborn

A Report of 4 Cases Treated Surgically[1]

by

TYGE CL. GERTZ

Judging from the few traces in the literature, little interest has been devoted to the subject of intestinal obstruction in the newborn in Denmark. In 1922 DAHL IVERSEN collected a total of 36 cases, the majority of which were from the Children's and Lying-in Departments of Rigshospitalet, Copenhagen. Some of them had been published previously, but only a few had been treated surgically, and only 1 with success (ERNST, 1916). In 1942 WINDFELDT brought this subject up again in connection with operations on 3 cases. In the interval and after the latter publication there was silence on the subject up to 1948, when WINKEL SMITH discussed the pathogenesis, diagnosis and treatment of malrotation, which he had treated surgically in a few instances. He did not, however, deal with other varieties of intestinal obstruction in infancy.

In the course of the last four—five months I have had occasion to treat 4 cases of intestinal obstruction, 1—8 days of age. In spite of the fact that they represented four different varieties of intestinal obstruction, the syndromes included so many similar features that I feel that the possibilities of a preoperative differential diagnosis and the aspects of treatment are worth considering.

In this way I hope to arouse interest in these lesions, the early diagnosis of which is of decisive importance to the successful out-

[1] The first 3 cases have already been reported in a paper read before the Pediatric Society on April 27, 1949.

come of surgical treatment, if attempted. It is true that the condition is uncommon, but not quite so uncommon as previously assumed. According to WINDFELDT there were 4 instances of atresia or ileus among a total of about 17 000 infants born in Lying-in Departments A and B during the period 1936—40, or an incidence of approximately 1 per 4 000. I am inclined to believe that the incidence is still higher, and my reasons are as follows. According to the annual reports of the municipal hospitals and Rigshospitalet in Copenhagen, a total of 15 infants suffering from intestinal atresia or other varieties of intestinal obstruction were admitted to the Children's Departments in Copenhagen from 1941—46. All of them died, presumably without operation. During the same period there was a total of 1 000 deaths of infants below 1 year of age in the same departments. As the infant mortality during this period was, according to LINDHARDT, between 45 and 50 per 1 000, of whom, however, 15 per cent died within the first 24 hours of life and were therefore probably not admitted to a Children's Department, these 1 000 deaths can probably be taken to represent a group of about 25 000 infants. As the cases of intestinal obstruction have probably not been overrepresented in the Children's Departments, this gives an incidence of ileus during infancy of 15 per 25 000 or 1 per 1 700. And this must no doubt be regarded a minimum figure, as a number of mild cases of malrotation are probably concealed under the diagnosis of vomitus.

My first patient was a boy 3 days of age, who had been transferred from a provincial hospital as suffering from congenital vitium recti. His birth weight was 3 000 g. He could not be induced to suck, and on the first day of life he began to vomit bile-coloured fluid. Two days after birth he passed sparse meconicum, but apart from that he had not had a motion. After admission to the Children's Department there were several non-explosive vomitings of bile-coloured substance. Palpation of the rectum gave the impression of a constriction about 7 cm above the anus. The abdomen was somewhat distended, particularly in the left side where the intestinal patterning could be traced. The turgor of the skin was slightly diminished, but otherwise the patient

was not debilitated. X-ray examination of the abdomen showed numerous large and small air-distended loops of the small intestine, in places with fluid levels (Fig. 1). Barium enema showed the colon to be exceptionally narrow, but there were no strictures and it was apparently empty. The x-ray diagnosis was low obstruction of the small intestine. Without making further attempts at detecting the cause of this obstruction, we decided upon operation. The upper loops of the small intestine were found to be dilated, air-filled and hypertrophic, narrowing evenly towards the ileocaecal junction without exhibiting an actual stricture or atresia. The terminal 25 cm of the ileum were, however, filled with a firm, pasty mass of a consistency almost like putty. These masses could hardly be shifted, and there was no doubt that the condition was a meconium ileus. The area immediately above the beginning of the pasty mass was punctured with a hypodermic needle, and after aspiration of some air 40 cc of a solution of pancreatin, hastily procured from the laboratory of the Children's Department, was injected. The site was sewn up with one catgut suture, the intestine was reduced and the abdominal wall closed. Even at that time it was felt that the firm masses had softened somewhat, and shortly after the patient was returned to the ward he passed meconium. A duodenal tube was inserted, and after the diagnosis had been confirmed by examination of the duodenal juice for trypsin, the infant was given alternately human milk and a solution of pancreatin through the tube. In addition, he was given repeated enemas of a solution of pancreatin. He did not spit or vomit after the operation, and the motions soon assumed the appearance of human milk stools. One month postoperatively there were again symptoms of intestinal obstruction. It was therefore necessary to embark upon another operation, as it was presumed to be a case of adhesive ileus. The operation confirmed this diagnosis. A number of partly strand-shaped, partly broad, flat adhesions between the loops of the small intestine as well as between the ileocaecal junction and the transverse colon had to be freed. The patient withstood this intervention also and did well afterwards, but of course he still required pancreatin in connection with meals. There were no signs of pulmonary complica-

tions, and at the present time the baby is more than 5 months of age and his development is normal.

Summary of the Case. A boy 3 days of age exhibited symptoms of intestinal obstruction from birth. Operation revealed a meconium obturation. After a solution of pancreatin was injected directly into the small intestine, the intestinal obstruction was rapidly relieved. The causative lesion, cystic fibrosis of the pancreas, could of course not be cured, and therefore the patient is given pancreatin as a substitute for the missing pancreatic enzymes.

The second patient was a boy transferred from Lying-in Department A to the Children's Department at the age of 3 hours. The delivery had been natural and the birth weight was 2 850 g. Half an hour after birth the child began to spit bile-coloured fluid. After admission to the Children's Department he went on spitting, but he also had several motions resembling meconium. X-ray showed obstruction of the small intestine in the uppermost loops, particularly in the duodenum. Consequently the diagnosis of malrotation was contemplated, although a barium enema showed a rather narrow but normally situated colon. As the infant was passing meconium and did not exhibit a typical clinical picture of ileus, it was decided to temporize until the following day. Renewed x-ray examination then showed a more marked intestinal obstruction (Fig. 2) and according to the radiologist there was a possibility of meconium ileus. As the clinical picture had also become more typical and the intestinal patterning stood out distinctly on the abdomen, operation was decided upon. In the lower ileum, a short distance from the ileo-caecal junction, there was an atresia. The continuity of the small intestine was preserved but the lumen was closed. The proximal sections of the bowel were greatly dilated, hypertrophic and filled with thin meconium and air, whereas the lower segments were collapsed and no thicker than a slate pencil. Saline solution injected into this area passed readily to the caecum, so it was considered that the atresia must be solitary. An antiperistaltic ileo-ileostomy was made of the two segments adjoining the atresia. It was constructed in two layers with a continuous seroserous stitch and running over-and-over stitch with the finest silk. Before the

anastomosis was closed the upper segment was largely emptied of meconium by suction. Immediately after the operation a thin catheter was passed into the stomach through the nose and suction was exerted, permanently during the first 24 hours, later intermittently, glucose solution and later human milk in small portions being given in the intervals. In addition the child received prostigmine in small doses and rectal injections of saline solution. It was not until the fourth day that he began having motions, but then the gastric aspirations could soon be discontinued and the catheter removed. After that all his food stayed down and he soon began to suck. Three weeks after admission he was discharged in a satisfactory condition. At an age of nearly 4 months x-ray showed a normal passage through the intestine.

Summary of the Case. The patient was a boy 3 hours of age who vomited bile from birth but also passed several motions resembling meconium. Operation on the second day of life showed a low-seated, solitary atresia of the small intestine. Ileo-ileostomy was constructed. The passage through the intestine was established on the fourth post-operative day and the course and development have been normal ever since.

The third patient was sent to the Children's Department via the Fuglebakken Children's Hospital in Copenhagen. He was a boy 6 days of age who was two weeks premature; his birth weight was 2 800 g. From the first day of life he spat, but there was no major vomiting. The stools were sparse, but were stated to bear the marks of human milk. On admission he was in poor condition, the turgor of the skin was reduced, and he had lost 350 g. The abdomen was fallen-in, if anything. X-ray showed dilatation of the stomach and duodenum, where most of the opaque medium ingested four hours earlier was retained. Still, scattered patches of the barium were discernible in the non-dilated small intestine (Fig. 3). A barium enema was not given. Malrotation was diagnosed and an operation decided upon, to be preceded by a blood transfusion and administration of parenteral fluid. On opening the abdomen, collapsed cyanosed loops of the small intestine were found. After eventration it was apparent that the entire small intestine as well as the caecum were twisted 360° clockwise around the base of the unattached mesentery of the midgut.

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

Detorsion was now performed and the adhesions were freed as recommended by LADD. Thereupon the intestine was replaced so that the course of the jejunum from the duodenum was towards the right iliac fossa, whereas the caecum and ascending colon were transferred to the left side of the abdomen. During the first postoperative days there was some spitting, and therefore a catheter was passed down into the stomach for purposes of intermittent suction. Otherwise the post-operative course was uneventful. Stools were passed as early as the second day, and on the third day the suction was discontinued. Nine days after the operation the patient was again transferred to the Fuglebakken Children's Hospital, whence he was discharged shortly after in a satisfactory condition.

Summary of the Case. A boy 6 days of age spat bile-coloured fluid from birth but also had motions bearing the marks of human milk, indicating that intestinal obstruction could not be complete. On admission he was dehydrated and on the whole in poor condition. Operation revealed a common and unattached ileocolic mesentery with volvulus of the midgut. After detorsion and freeing of the adhesions by LADD's method the passage through the intestine was soon established and became normal.

The fourth and last patient was a girl, transferred to our Department at the age of 7 days from the Children's Department of the Copenhagen County Hospital in Gentofte, where she had been staying for a few days. Her birth weight was 3 700 g, but on admission she weighed only 3 300 g. She had been spitting bile-coloured fluid from birth. Nevertheless her appetite had been good, but the feedings were followed by almost explosive vomiting. The passage through the intestine had been patent, as the patient had passed stools bearing the marks of human milk. At the County Hospital a barium meal had shown that the stomach was of normal size and shape, but that the entire duodenum was greatly dilated. Twenty-four hours later a great part of the barium remained in the stomach and duodenum, though part of it had passed further on, being scattered in lumps in the non-dilated small and large intestine (Fig. 4). A tentative diagnosis of malrotation or duodenal stricture was made and the

patient was transferred to us for operation. On admission she was flaccid, showing reduced turgor of the skin and marked jaundice. A plasma transfusion was therefore administered before the operation. She latter revealed a collapsed but not particularly narrow small intestine and a normally placed colon. Eventration of the small intestine exposed the duodenum and the adjacent part of the jejunum, both of which were enormously dilated, projecting down below the mesentery. The transition to the collapsed area was abrupt, but there was no stricture at the site and no external strands of adhesion to account for the obstruction. It was therefore considered that there must be a diaphragm with a minute but permeable opening. An antiperistaltic jejunojejunostomy was made of the two segments adjoining the site of obstruction. The technique was as in the case of atresia. Twelve hours after the operation an attempt was made at feeding the infant, but as this induced bile-coloured vomiting a gastric tube was inserted and used alternately for aspiration and administration of human milk in increasing doses. As early as the second day more stayed down than the amount aspirated, and on the third day the passage through the intestine was established. The aspirations could soon be discontinued. On discharge, 17 days after the operation, the baby was doing well. X-ray on the previous day showed some dilatation of the duodenum, which did not empty until seven hours after ingestion of the barium, but otherwise the passage was natural.

Summary of the Case. A girl 7 days of age suffered from bile-coloured spitting and explosive vomiting after feedings from the first day of life but passed stools bearing the marks of human milk. X-ray showed marked dilatation of the entire duodenum. Operation revealed a stricture, presumably a diaphragm, immediately distal to the duodenojejunal junction. After jejunojejunostomy the intestinal passage was soon established and the infant was discharged 17 days later in a satisfactory condition.

A common feature of all 4 cases was bile-coloured spitting setting in immediately or shortly after birth, indicating an obstruction distal to the papilla of Vater. The 2 last-mentioned cases differ from the former, however, in that they had a rather more

protracted course. Both took some food during the first days of life, but judging from their poor condition on admission, they had probably not retained much of the ingested food. Still, both had passed human milk stools, whereas the other 2 had passed only sparse amounts of meconium. Moreover, there was an objective difference, i. e. in the abdomen, which if anything was fallen-in and only slightly distended in the epigastric region, whereas the first 2 patients had exhibited meteorism with a more or less marked patterning. The x-ray signs also permit classification into two equal groups. The first 2 cases exhibited dilated loops of the small intestine and fluid levels, i. e. a picture typical of obstruction in the small intestine (Figs. 1 and 2). In the latter cases, on the other hand, the small intestine was practically collapsed, containing only small amounts of gas, whereas the stomach and particularly the doudenum were greatly dilated (Fig. 3). The barium meal was retained for a long time, but some of it did pass, being discernible in scattered lumps in the small and large intestine. Barium enemas were given only in the first 2 cases (*vide infra*). In the last 2 cases the most probable diagnosis was considered malrotation attended with volvulus, which was also contemplated in the case exhibiting a stricture. No doubt an accurate diagnosis could have been made before operation if a barium enema had been given. This would at least have revealed the abnormal situation of the ascending colon and the caecum in the case of malrotation. In the case of the stricture so much of the opaque medium had passed into the colon that its outlines were faintly discernible, and judging from the appearances, its position was normal (Fig. 4). This is of course easy to say now when the diagnosis has been confirmed by operation, but a barium enema would probably also have confirmed it. In the first 2 cases an accurate diagnosis was not made, but as mentioned above, in the case of atresia the possibilities of malrotation and later of meconium ileus were considered. There are, however, so striking and characteristic differences between these conditions that the differential diagnosis could have been made preoperatively if they had been borne in mind. The plain film of the patient with atresia revealed numerous typical fluid levels (Fig. 2), whereas

the case of meconium ileus exhibited only a few fluid levels in the uppermost loops, while the lower, most dilated loops of the small intestine were devoid of fluid levels, and gradually also of air, although their appearance was slightly patchy, as if there were bubbles of air in the contents (Fig. 1). This accords well with the fact that the intestinal contents in meconium ileus are sticky and viscid, whereas in atresia they are of a normal fluid consistency. The barium enemas also revealed marked differences between the two cases. In the case of atresia the colon was of normal dimensions, becoming completely filled, and, a matter of the utmost importance, the barium entered the lower loops of the ileum. The lastmentioned phenomenon appears to be incompatible with meconium ileus. In the case with this latter condition the colon was extremely narrow and the opaque medium could not even be forced as far as the splenic flexure, presumably because the remainder of the colon was filled with meconium.

Evidently a definite differential diagnosis could have been made in all 4 instances by means of a plain film of the abdomen combined with a barium enema. Barium by mouth, on the other hand, appears to be of doubtful value, as also in cases of intestinal obstruction in adults. In fact, this form of examination should be avoided as it may involve a certain risk, i. e. the barium may give rise to difficulties in the intestinal passage during the postoperative course, and vomiting, if any, may result in aspiration of barium to the lungs.

In the first 2 instances the differential diagnosis might have been made in the laboratory. FARBER has advocated a simple method of examining the meconium for cornified epithelial cells. The absence of these cells should be suggestive of atresia. It is, by the way, strange that patients with an atresia are able to pass meconium at all, a fact which may be rather confusing but which is worth bearing in mind. According to FORSSNER's theory on the pathogenesis of atresia, which I do not propose to dwell on in detail, the condition is presumed to arise as early as in the third—fourth week of foetal life, whereas the production of bile is not started until the third—fourth month. The explanation given by FORSSNER of meconium below the atresia is that the

latter does not become complete until later. In our case this explanation sounds very plausible, as the continuity of the intestine was not interrupted, only the lumen. Farber's test was not performed in any of our cases. — Another possible means of obtaining an early differential diagnosis is to examine the duodenal juice for trypsin. If a drop of duodenal juice is placed on the gelatinous coating of an x-ray film the tryptic activity will rapidly digest this coating, leaving a transparent patch. This test was made in our case of atresia, and we were therefore warned beforehand that it could not be a case of meconium ileus. In the case of meconium ileus this test was not made until after the operation.

As regards the operative procedure I shall not dwell on the treatment of malrotation, but just refer the reader to LADD's fundamental work on this treatment (described in detail in the above-mentioned paper by WINKEL SMITH). In our case the operation consisted primarily in a detorsion, whereupon the ectopic caecum and ascending colon were freed in order to avoid a recurrence.

Successful operations of atresia of the small intestine have not been published before in Denmark, but as mentioned above, FRNST operated successfully upon a case of atresia of the duodenum in 1916, one of the first reports to be found in the world literature. In 1941 WINDFELDT reported a case of atresia of the small intestine submitted to jejunosigmoidostomy, but the patient died on the following day. As far as I know this is the only Danish case in which primary anastomosis has been attempted. A few patients have been subjected to enterostomy, but all have died shortly after. On the other hand, foreign literature, particularly American, contains quite a number of successful operations, mostly from recent years. Up to 1941 LADD operated upon a total of 34 patients with atresia of the ileum, of whom only 3 survived. In 9 instances he did ileo-ileostomy or ileocolostomy with 2 survivors, whereas enterostomy was done in 20 cases, all of whom died. LADD's cases are, however, derived from a long period. The considerably improved prognosis of latter years is apparent from a recent paper by POTTS. Within a short space

of time he has operated upon a total of 5 cases with atresia of the intestine at various sites. Of these 4 have survived the intervention, which in all cases consisted of anastomosis. The site of the atresia was in the ileum in 3 cases, all of whom survived.

The successful outcome of the operation in our case is no doubt due largely to the fact that we received the patient for operation as early as the second day of life. The longer the period elapsing from birth until operation, the more bursting will the bowel above the atresia be. This may partly cause difficulties in connection with the construction of an anastomosis, if any, partly involve the risk of nutritive disturbances with perforation of the gut above the atresia. I am, moreover, inclined to attach the utmost importance to maintenance of permanent and later intermittent suction during the first four postoperative days. It goes without saying that one must allow for some time before the passage through the completely collapsed intestine below the atresia is established. If the upper intestine is not kept clear all the time, there is risk that the sutures may burst and also that there may be local necrosis and perforation in the lowest part of the dilated small intestine, the usual outcome in non-operated cases. The operation should always consist in a side-to-side anastomosis. According to experience gained elsewhere, mere enterostomy will practically always end fatally. Of course, it is essential to make sure that the condition is not multiple, but this is not particularly common. According to a large statistic material quoted by WINDFELDT, multiplicity is encountered in about 18 per cent of the cases. The fluid balance must be watched carefully, in particular during the first postoperative days when practically no food can be administered.

As to intestinal stricture, at least when it is marked enough to give rise to obstruction the treatment is very similar to that of atresia, i. e. a side-to-side anastomosis past the constricted area as soon as the condition has been diagnosed. In a few instances of a less marked stricture, the condition may, however, remain undetected for years. Among LADD's 22 cases 4 did not arrive for operation until they had passed the first year of life; one of them was as old as 9 years of age before his symptoms grew so

marked that a diagnosis was made. From Denmark 1 case of this nature operated on at the age of 6 years by P. N. HANSEN has been reported by MONRAD and 1 operated on at the age of 2 1/2 years by KJAERGAARD by CLAUSEN. No case, however, has been reported hitherto in which operation had to be carried out shortly after birth.

In the great majority of cases a stricture is situated in the duodenum, whereas atresia is usually found in the ileum, so the localization was typical in both our cases.

Little appears to have been written about the treatment of meconium ileus. Attempts at emptying the sticky, viscid meconium through an enterostomy or through multiple punctures of the bowel have seldom led to the desired result. It is only recently, since the relationship of the condition to cystic fibrosis of the pancreas has become accepted, that adequate methods of treatment have been suggested, mainly by DOROTHY ANDERSEN and FARBER. The abnormal consistency of the meconium is due to the absence of pancreatic ferments. Normally the meconium is semi-fluid, but in these cases it is sticky, viscid, almost pasty. The rather weak peristalsis during foetal life is therefore unable to propel this mass through the intestine. It becomes ever more inspissated, finally occluding the lumen completely, most frequently in the distal, narrow part of the ileum and the proximal segment of the colon. In other words, the intestinal obstruction is congenital.

It has been demonstrated by FARBER that meconium from children dying of meconium ileus may be reduced to a semi-fluid and natural consistency in the course of few hours by the action of pancreatic enzymes. He has therefore suggested washing the intestine by injecting a solution of pancreatin through an enterostomy. He states that this method was used in four instances by GROSS, who succeeded in relieving the mechanical obstruction of the intestine but lost all his patients shortly after the operation from intercurrent infections. The writer has been unable to find GROSS' original report, so that no further details are available.

WINKEL SMITH once tried operation by the method of GROSS, but the inserted drain eroded the intestinal wall and the child

died a few days postoperatively of peritonitis without having exhibited intestinal passage. At the postmortem examination the intestinal contents were, however, seen to be semi-fluid. Bearing this in mind I did not feel at all like making a similar attempt, but at the suggestion of the pædiatricians present I consented to try the above-mentioned injection of pancreatin. If this failed, it was my intention to perform another operation to construct an enterostomy. Of course, it is impossible to say whether this infant might have been saved even without operation. It received energetic postoperative treatment with a solution of pancreatin injected through a duodenal tube and pancreatin enemas, but as already mentioned, the intestinal passage was established in immediate connection with the operation. As this is the least exacting method, it is worth trying, but I think that it is wise to inject more than I did and to distribute the injections over several areas of the intestine. In case of failure, re-operation may be attempted and an enterostomy constructed for the purpose of a more effective treatment. This presupposes, however, that diagnosis has been made prior to the operation, as a solution of pancreatin is not normally available, but as evident from what has been said above, a pre-operative diagnosis should be possible in the majority of cases.

It remains an open question whether the surgeon is doing these children a favour in tiding them over the intestinal obstruction. Nothing can be done about the cystic fibrosis of the pancreas and they must be given pancreatic ferments in connection with their meals for the rest of their lives. It is not yet known whether this saves them from the pulmonary complications to which most children with pancreatic fibrosis succumb. As mentioned above, our patient has not yet exhibited signs of pulmonary complications. He is doing well at the age of nearly 6 months.

Summary

Four cases of intestinal obstruction in infancy are presented. All the babies underwent operation and all recovered. In one instance the obstruction was due to atresia of the ileum, in another

to a stricture immediately distal to the doudenojejunal junction. Side-to-side anastomoses were constructed in both. The third case was one of meconium ileus and the intestinal passage was established after injection of a solution of pancreatin into the small intestine. The fourth case had a common ileocolic mesentery attended with volvulus of the midgut and recovered after detorsion of the volvulus followed by freeing of the adhesions in accordance with LADD's method. On the basis of these 4 cases the writer discusses diagnosis and differential diagnosis in intestinal obstruction during infancy, emphasizing particularly the importance of x-ray examination.

Resumé

On nous présente ici quatre cas d'obstruction intestinal chez des enfants en bas âge. Les quatre bébés furent opérés et guérirent tous. Dans le premier cas l'obstruction était due à une atrésie de l'ileum, dans le second à une stricture immédiatement distale à la jonction duodénojéjunale. Les anastomoses latéro-latérales ont été faites dans les deux cas. Le troisième cas était un ileus méconial oú le passage intestinal fut établi par une injection de solution de pancréatine dans l'intestin grêle. Le dernier cas enfin, présentait un mésentère iléocolique commun adhérent à un volvulus de mésogastre, et guérit après la détorsion du volvulus suivie du décollement des adhérences, suivant la méthode de LADD. Se basant sur ces quatre cas, l'auteur nous parle du diagnostic ainsi que du diagnostic différentiel de l'obstruction intestinal dans l'enfance, en insistant particulièrement sur l'importance de l'examen radioscopique.

Zusammenfassung

4 Fälle von Darmverschluss im Kindesalter sind beschrieben worden. Alle diese Kleinkinder wurden operiert und alle sind geheilt. In einem der Fälle bestand der Verschluss auf Grund einer Atresie des Ileum, in einem anderen auf Grund einer Striktur unmittelbar distal von der Duodeno-Jejunal-Verbindung. Bei beiden wurde Seit-zu-Seit-Anastomose angelegt. Der dritte Fall

war ein Mekonium-Ileus und die Darmpassage war nach einer Injektion einer Pankreatinlösung in den Dünndarm wiederhergestellt. Der vierte Fall hatte eine Mesenterium ileo-colicum commune mit Volvulus des Mesogastriums und wurde wiederhergestellt durch Detorsion des Volvulus mit nachfolgender Lösung der Adhäsionen nach der Methode von LADD.

Auf Grund dieser 4 Fälle bespricht der Autor die Diagnose, und Differentialdiagnose des Darmverschlusses bei Kindern und weist nachdrücklich auf die Wichtigkeit der Röntgenuntersuchung hin.

Resumen

Se presentan cuatro casos de obstrucción intestinal en niños de corta edad. Los cuatro bebés fueron operados y curaron todos. En el primer caso la obstrucción era debida a una atresia del íleon; el en segundo a una estructura inmediatamente distal a la unión duodenoyeyunal. Se han construído en los dos anastomosis una al lado de otra. El tercer caso presentaba un íleon meconial y el pasaje intestinal fué establecido por una inyección de solución de pancreatina en el intestino delgado. Finalmente, el último caso presentaba un mesenterio ileocecal común adherente a un vólvulo de mesogástrico, que curó después de la detorsión del vólvulo seguida de un desprendimiento de las adherencias, siguiendo el método de LADD. Basándose en estos cuatro casos, el autor nos habla sobre la diagnosis, así como de la diagnosis diferencial de la obstrucción intestinal en la infancia, insistiendo particularmente en la importancia del examen por rayos X.

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(FROM THE CHILDREN'S HOSPITAL, MARTINSVEJ, COPENHAGEN.
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A Simple Method of Estimating the Inulin and Para-amino-hippurate Clearances in Newborn Infants[1]

By

JØRGEN VESTERDAL

The inulin clearance in infants was first measured on patients with inoperable meningomyeloceles (8, 12, 13). Using an intravenous drip, inulin was injected into the tubing and afterwards estimated in samples of urine and of blood from the anterior fontanelle. The same technique was later used for the estimation of diodone and inulin clearances (4).

Recently, studies on these clearances in normal infants have been published by BARNETT & *al.* (1), who used paraamino-hippurate (PAH) and inulin but do not describe their technique, and by WEST, SMITH & CHASIS (11) who gave PAH and mannitol by intravenous infusion and measured their concentrations in samples of catheter urine and venous blood.

Since it may be difficult to draw four—five blood samples from the veins of a newborn infant during the experiment, a micromethod for the estimation of the agents in capillary blood was desirable.

Preliminary experiments (10) showed that intravenous infusion should be avoided, as the increased diuresis may influence the kidney function.

I have therefore used a simple method in which inulin and PAH are injected subcutaneously and estimated in capillary blood and in urine by a microtechnique.

Intravenous fluid may be given in varying doses independent of the administration of PAH and inulin. The method is not

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suitable for estimating the maximal tubular excretory mass, Tm_{PAH}.

Subcutaneous administration of inulin and diodrast was used by FINDLEY & WHITE (5) and HILDEN (6) and of inulin and PAH by BRUN, HILDEN & RAASCHOU (3).

I have used the Swedish inulin »Astra» (a 10 % solution) and a 3 % solution of sodium p-amino-hippurate prepared from p-amino-hippuric acid which was most kindly supplied by the Leo Chemical Factories, Copenhagen.

For infants under 3 weeks of age, 10 ml of each solution is a suitable dose, independent of the infant's weight, and for infants aged between 3 weeks and 2 months, 15—20 ml of each solution were used. The inulin solution must be heated in boiling water for at least 15 minutes until it is completely clear, lest pyrexia or even abscesses due to incomplete absorption occur.

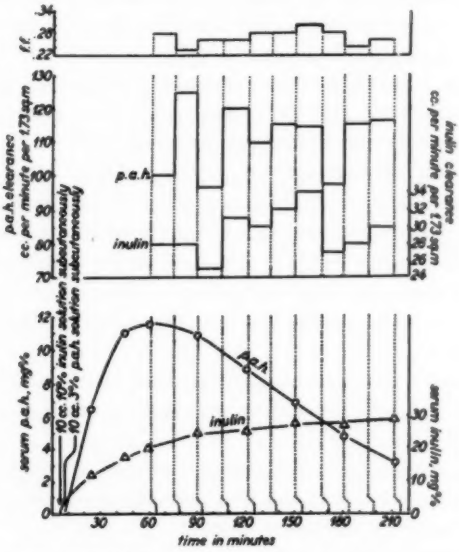

Fig. 1. Girl 17 days old, birth weight 3 500 g. Curves respresenting plasma inulin and PAH after subcutaneous administration. The inulin clearance, the PAH clearance and the filtration fraction (f. f.) are shown in the upper part of the figure (drawn with different scales and zero points).

The plasma inulin and PAH curves obtained from one experiment are seen in Fig. 1. The PAH curve reaches its peak early and falls in an almost straight line which is suitable for the clearance estimation. The inulin curve has no peak and the concentration is nearly constant during the experiment.

The blood samples are drawn from the heel into heparinized test tubes. 0.2 ml plasma is sufficient for a double assay of both inulin and PAH. The wound must bleed freely. Pressing on the foot must be avoided, as pain may cuse a reflex contraction of the kidney vessels.

Analytical Method

The plasma proteins are removed by a Zomogy precipitation. To 1.6 ml Zomogy zinc sulfate solution 0.2 ml plasma and 0.2 ml Zomogy sodium hydroxyde solution are added. These are mixed well and allowed to stand overnight. Hereafter the mixture is centrifuged and the PAH and inulin in the supernatant fluid estimated.

A similar precipitation is carried out on the urine samples in order to remove chromogens, which may interfere with the inulin assay.

For the PAH estimation precipitation with a mixture of 40 ml p-toluol-sulfonic acid and 60 ml 2 N hydrochloric acid was tried, but it was found impossible to get completely clear protein-free fluid in this way.

Estimation of PAH

BRATTON & MARSHALL JR.'s method (2) for the estimation of sulfonamides was used in the following modification (by C. C. JENSEN, personal communication).

To 0.300 ml of the protein-free solution, 0.100 ml 2 N hydrochloric acid and 0.025 ml of a 0.2 % freshly prepared solution of sodium nitrite were added. The mixture was shaken and allowed to stand for three minutes. 0.025 ml of a 0.5 % amidosulfonic acid solution was added and the mixture shaken and allowed to stand for three minutes. 0.250 ml of a 0.25 % solution

of N-ethyl-α-naphthylamine hydrobromide in ethyl alcohol was added. The whole was shaken and allowed to stand for 30 minutes before colorimetry.

Colorimetry. A Lumetron Photometer 402-E with microcuvettes for 0.5 ml fluid with a fluid thickness of 0.5 cm was used with a green filter (530 mμ). Distilled water was used for the blank value.

The result was read on a standard curve. The standard curves for plasma and water were not identical, owing to a small loss of PAH in the precipitation (about 3 %).

Estimation of Inulin

KRUHØFFER's method (7) was used in the following modification.

The reagent is prepared by dissolving 100 mg resorcin in 50 ml 98.5 % ethyl alcohol and adding 50 ml concentrated hydrochloric acid (this acid must be very pure). The mixture is well shaken and cooled in water. The reagent (as well as resorcin itself) is very sensitive to light and must be freshly prepared.

0.250 ml of the pretein-free fluid is pipetted into a small glass flask with a glass stopper and 0.500 ml of the reagent is added (by means of a Krogh syringe pipette, as the reagent is rather viscous). The mixture is heated in a waterbath at 80° C. (± 0.5°) for 35 minutes. After cooling in water the flasks are kept in darkness for one and one-half hours before colorimetry.

Colorimetry. The microcuvettes already mentioned were used with a blue-violet filter (440 mμ).

The result was read on a standard curve. The curves for plasma and water (or urine) were not quite identical, as the glucose in plasma reacts with the resorcin reagent, giving a difference of about 1 mg % in the inulin concentration. When the inulin concentration in plasma is about 25 mg % — the usual level — variations in the blood sugar may be disregarded.

Accuracy of the Analytical Methods

The PAH Determination. The standard deviations shown in Table 1 have been calculated from 285 double assays. It will

Table 1

PAH Concentration in Sample (mg %)	Standard Deviation (mg %)
0 — 1.3	0.06
1.3— 2.8	0.08
2.8— 4.6	0.10
4.6— 6.7	0.09
6.7— 9.3	0.11
9.3—12.4	0.10
12.4—16.7	0.12
16.7—21.6	0,19
>21.6	c. 0.23

be seen that the standard deviation is generally about 0.1 mg %. The standard deviation expressed in per cent of the concentration in the sample is shown in Table 2. It will be seen that the accuracy decreases rapidly with small concentrations.

Table 2

PAH Concentration in Sample (mg %)	Standard Deviation in per cent of Concentration
< 1	>6.5
1— 2	6.5—4
2— 3	4 —3
3— 5	3 —2
5—10	2 —1
>10	c. 1

For the clearance determination, the PAH concentration in plasma has to be below the self-depression limit. In adults this value is between 7 and 13 mg % PAH in plasma (3). The value for infants has not been reported. It seems to be a little lower (5—10 mg %). It is therefore necessary to use concentrations below 5 mg % in order to avoid self-depression. BARNETT & *al.* (1) used concentrations below 2 mg %.

The Inulin Determination. The standard deviations in Table 3 have been calculated from 91 double assays. In the range 12—50 mg %, which is generally used, the standard deviation is about 5 % of the concentration in the sample.

Table 3

Inulin Concentration in Sample (mg %)	Standard Deviation (mg %)
0 — 9.5	0.3
9.5—16	0.6
16 —24	1.1
24 —33	1.5
33 —45	1.7
45 —63	2.3

Catheterization

As micturition often occurs in infants when the genital region is cleansed and the tip of the catheter is introduced into the external orifice of the urethra, permanent catheterization is necessary, and this is also very useful in experiments with many clearance periods.

The technique is very simple in female infants: a smooth rubber catheter no. 10—12 is introduced into the bladder and fixed on either side of the vulva by a string and adhesive plaster. Apparently it does not disturb the infant, who usually sleeps during the experiment. Crying babies must be soothed by feeding. If they are not quiet, fallacious results may be obtained, owing to reflex contraction of the renal vessels (as demonstrated in adults (9)).

The bladder is emptied completely by washing twice with 5 ml sterile saline and once with 5 ml air.

In order to avoid urinary infection, a single dose of sulfathiazole and penicillin was given after the experiment.

With boys it is less easy to obtain successful experiments, partly because it is more difficult to empty the bladder completely, and partly because catheterization always causes pain in boys.

In calculating the clearances a delay time of three minutes, *i.e.* the time between the production of the urine in the kidney and its flowing out of the catheter, must be allowed (see Fig. 1).

Summary

A method of determining the inulin and paraamino-hippurate clearances in newborn infants is reported.

The agents are injected subcutaneously and estimated in samples of catheter urine and capillary blood by a microtechnique.

The accuracy of the analytical method is, with the concentrations commonly used, about 5 % for inulin and 2—6.5 % for PAH.

Résumé

Une méthode pour déterminer la précipitation de l'inuline et du para-amino-hippurate chez lex nouveau-nés est rapportée. On fait des injections sous-cutanées des agents et on les évalue en épreuves d'urine prise à la sonde et de sang capillaire par un procédé micro-technique. La précision de la méthode analytique est, avec la concentration ordinairement utilisée, d'environ 5 % pour l'inuline et de 2—6.5 % pour le PAH.

Zusammenfassung

Es wird berichtet über eine Methode zur Bestimmung des Inulin und Para-amino-hippurat Verhaltens bei Neugeborenen. Nach subkutaner Injektion des Agentien wurde der Inhalt mikrotechnisch in Katheterurinproben wie auch in Kapillarblut bestimmt. Die Genauigkeit der analytischen Methode ist mit den gewöhnlich benutzen Konzentrationen c:a 5 % für Inulin und 2—6.5 % für PAH.

Resumen

Se da cuenta de un método para determinar la precipitación de inulina y de para-amino-hipúrico en niños recién nacidos. Los agentes se inyectan subcutáneamente y se evaluan en pruebas de orina sacadas a la sonda y de sangre capilar por un procedimiento microtécnico. La exactitud del método analítico, con las concentraciones generalmente utilizadas, oscila alrededor del 5 % para la inulina y del 2 al 6.5 % para el PAH.

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(FROM THE CHILDREN'S HOSPITAL, MARTINSVEJ, COPENHAGEN.
CHIEF: A. ROTHE-MEYER, M. D.)

Studies on the Kidney Function in Premature and Full-Term Infants by Estimation of the Inulin and Paraamino-Hippurate Clearances[1]

By

JØRGEN VESTERDAL and FOLKE TUDVAD

Only a few reports of investigations into the kidney function in newborn premature and full-term infants have been published.

The estimation of the filtration rate and the effective renal blood flow (*i.e.* the volume of blood passing through the active parts of the kidneys per minute) is most important. The filtration rate is considered to be identical with the inulin clearance. Mannitol clearance has also been used, but the results are not identical with those obtained with inulin clearance, the ratio mannitol clearance / inulin clearance being 0.902. The effective renal blood flow is measured by estimation of diodone (diodrast) clearance or paraamino-hippurate (PAH) clearance, which give identical results.

The normal values for adults are: inulin clearance 124 ml, and PAH clearance 648 ml per minute for a surface area of 1.73 sq. m. (7). The filtration fraction (*i.e.* the ratio inulin clearance / PAH clearance) is 0.192.

The first investigations on the kidney function in infants (1, 5, 13) showed that the clearances for inulin, urea, Na, K and Cl are very low.

Recently, a few thorough studies have been reported.

[1] Supported by a grant from King Christian X's Foundation.

In infants aged 2—4 days with inoperable meningomyeloceles, DEAN & MCCANCE (6) found the inulin clearance to be 16—45 ml and the diodone clearance 24—125 ml, both values corrected to a surface of 1.73 sq. m. The filtration fraction was 0.30—0.72, the average being 0.43.

BARNETT & *al.* (4) studied the kidney function in premature infants weighing between 2156 and 2470 g. Between the ninth and twenty first days the average inulin clearance was 4.4 ml, and between the ninth and fourteenth days the average PAH clearance was 13.2 ml (these two values have not been corrected for surface area). The average filtration fraction was 0.34.

In another paper (2) these authors compared two age groups of premature infants with birth weights between 2130 and 2520 g and found the following average values (corrected to a surface of 1.73 sq. m.): in Group A (3—13 days old) the inulin clearance was 48 ml and the PAH clearance 149 ml; Tm_{PAH}, *i.e.* the tubular excretory maximum for PAH, was 12.9 mg/min. In group B (49—107 days old) the inulin clearance was 67 ml and the PAH clearance 201 ml, and Tm_{PAH} was 20.8 mg/ml. The filtration fraction was 0.27—0.42, the average being 0.33, without difference between the two groups.

WEST, SMITH & CHASIS (18) studied the mannitol and PAH clearances and Tm_{PAH} in normal infants aged 1/2—110 weeks. In the first week of life the PAH clearance was about 100—130 ml (this and the following values have been corrected to a surface of 1.73 sq. m.). The adult value (per 1.73 sq. m.) was attained at the thirtieth week or later. Tm_{PAH} was 7—25 mg/min per 1.73 sq. m. in the first week of life, and the adult value, 77.5 mg/min, was reached in the thirtieth week. Mannitol clearance in the first week was about 25—60 ml, and the adult value was reached at 10—20 weeks. (As already mentioned, the mannitol clearance is not identical with the filtration rate.) The ratio mannitol clearance/PAH clearance was higher than the adult value during the first year.

Some authors (5, 13, 19) have found that the filtration rate decreases when the diuresis is low.

Authors' Experiments

Using the technique described in a previous paper (17), we have performed 55 experiments (16 with inulin, 2 with PAH, and 37 with simultaneous determination of inulin and PAH clearance). 15 experiments had only 1—3 diuresis periods each; the rest had 10—15 periods each.

The infants were 1—118 days old, with birth weights ranging from 1100 to 3750 g.

A preliminary report was published in 1948 (16).

Results

I. PAH Clearance. In our experiments, the self-depression limit varied between 5 and 10 mg % PAH in plasma.

Using periods where the PAH concentration in plasma was 1—5 mg % (in a few cases a little higher), we obtained the results shown in Fig. 1. The PAH clearance was very low in the first days of life (50—60 ml/min per 1.73 sq. m.), but increased rapidly

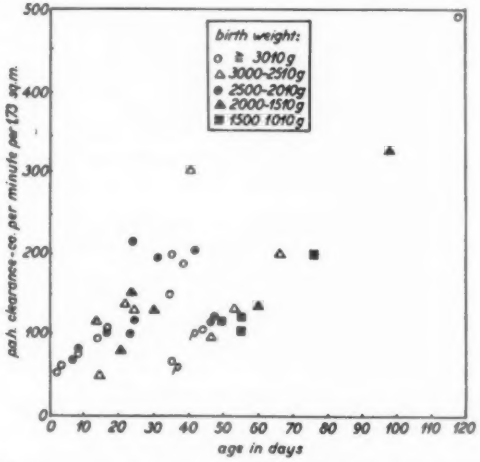

Fig. 1. PAH clearance in premature and full-term infants, corrected to a surface of 1.73 sq.m. The values marked P are discussed in the text of Fig. 3.

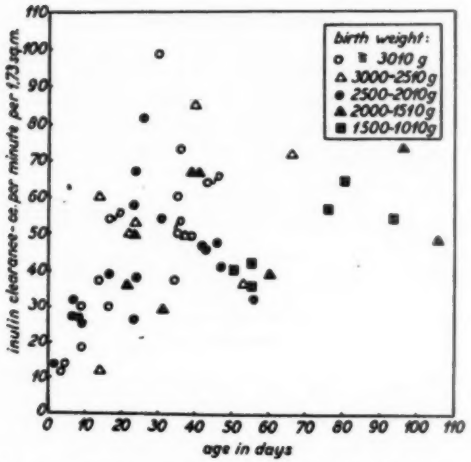

Fig. 2. Inulin clearance in premature and full-term infants, corrected to a surface of 1.73 sq.m. The values marked P are discussed in the text of Fig. 3.

during the first weeks, though with great individual variations. In the first three months it reached only half the adult value. One infant aged 118 days had a clearance of 497 ml.

There was no significant difference between the values of full-term infants and premature infants with birth weights over 1500 g. The clearances in infants with birth weights below 1500 g were all very low, but not definitely outside the ranges for full-term infants.

II. The Inulin Clearance (Fig. 2) was 12—14 ml/min per 1.73 sq. m. in the first days of life and, like the PAH clearance, it increased considerably in the first weeks, though with great individual variations. The adult value was not reached within the first four months. Values as high as 82 ml were seen as early as the twenty sixth day.

Here, too, there was no significant difference between the values of full-term infants and of premature infants with birth weights over 1500 g. The values of infants with lower birth weights were rather low, but not definitely outside the normal ranges.

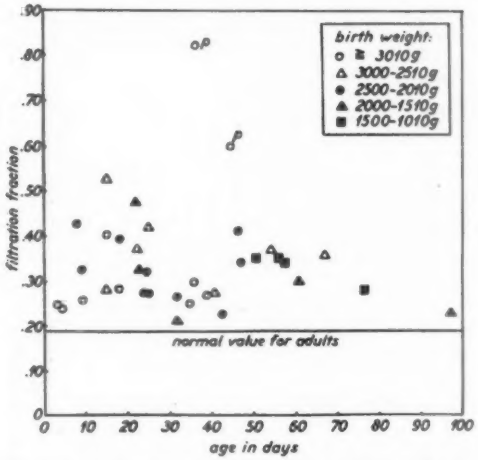

Fig. 3. Filtration fraction in premature and full-term infants. The values marked P in this and the preceding two figures were obtained from a mongolian idiot. They are probably pathological.

III. The Filtration Fraction (Fig. 3) was higher than the adult value in all of the experiments. There was no correlation between the filtration fraction and the birth weight or age in the first four months.

The values marked P in Fig. 3 are discussed later.

IV. Other Observations

(a) Depression of the clearances by pain was seen in a few cases. The filtration fraction remained almost constant during the depression (Fig. 4). In only 1 case was an increase in the filtration fraction seen.

The pain may have been caused by taking the blood samples from the heel. In most cases, however, this procedure affected the kidney function little or not at all. Subcutaneous administration of saline or glucose solution generally caused a considerable depression of the clearances which was followed by a return to normal values, sometimes with a short intervening stage of »supernormal» values.

(b) Variations in the clearances due to administration of

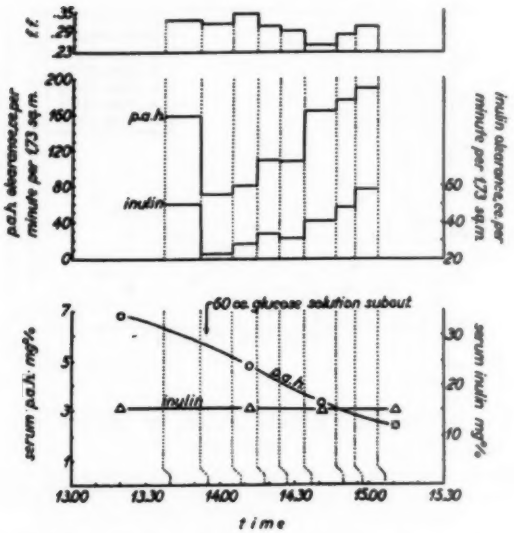

Fig. 4. Pain reaction. Inulin and PAH clearances are depressed at the time when the fluid is injected subcuteneously. The filtration fraction (f. f.) is almost constant.

water, *i.e.* dependence of the clearances on the diuresis, were studied in a number of experiments, but there is some difficulty in interpreting the results, as incomplete emptying of the bladder will cause proportionate variations in the diuresis and in the inulin and PAH clearances. Only experiments with uniform variations in a number of consecutive clearance periods are reliable in this respect.

Subcutaneous fluid administration was tried, but had to be abandoned because of the slow absorption of the fluid and because the variations in the clearances due to pain interfered with the variations caused by the fluid administration.

Fluid was therefore given by intravenous drip in a series of experiments. Altering the speed of infusion caused quite wide variations in the diuresis. In 23 of the experiments the diuresis increased to more than five times (in some cases even

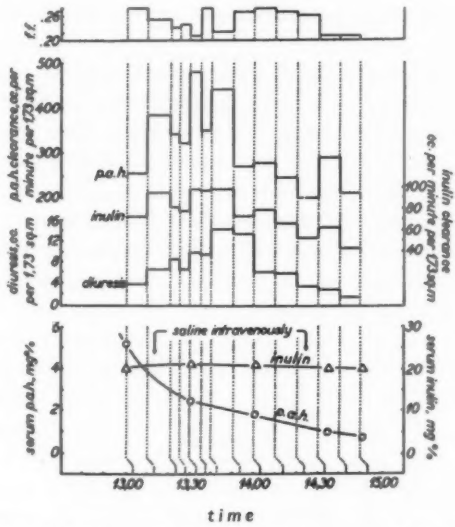

Fig. 5. The diuresis is increased by means of intravenous fluid administration. Simultaneously, the inulin and PAH clearances are increased while the filtration fraction (f. f.) is almost constant.

to more than ten times) the initial value, which was 0.6—4.9 ml/min per 1.73 sq. m. (average: 1.7 ml). In most cases the diuresis decreased again towards the end of the experiment to approximately the initial value. Experiments with pronounced clearance depressions due to pain were omitted from this series.

In 9 cases an increase of 50—100 per cent in both inulin clearance and PAH clearance was seen, with almost constant filtration fraction. One of these experiments in shown in Fig. 5.

In 4 cases only a slight effect was seen, and in the remaining 10 cases either no effect on the clearances was observed, or the variations observed might have been due to faulty emptying of the bladder.

The increase in the clearances due to fluid administration had no correlation with age or birth weight.

In a few cases a transitory increase in the clearances was seen when the diuresis increased to a higher value, but when

the higher diuresis was maintained the clearances decreased to their former value.

(c) Pathological findings. The values marked P in Figs. 1, 2 and 3 were found in a mongolian idiot with a birth weight of 3700 g. The filtration fraction was higher than that observed in the other infants, which may have indicated either a pathological condition or a higher degree of immaturity of the kidney (probably the latter). Microscopic examination of the urine revealed nothing abnormal, and the urine did not contain protein or sugar. In this infant there was a great increase in the clearances with increased diuresis.

In the series two other mongolian idiots are included. Their kidney functions did not differ from those of the normal babies.

Discussion

Using a simple technique which was applicable even to premature babies, we have found, in agreement with other authors, that the function of both glomeruli and tubuli is very low during the first days of life (even when corrected to a surface of 1.73 sq. m.). During the first weeks both functions increase rapidly, though with great individual variations. The adult values (per 1.73 sq. m.) were not attained within the interval covered by these experiments (1—118 days).

The filtration fraction is definitely higher in infants than in adults, indicating that the function of the tubuli is more immature than that of the glomeruli, although at birth the glomerular tuft is covered by a high epithelium (11, 8, 14, 9). The epithelium gradually changes to the squamous type, beginning in the medullary layer of glomeruli and progressing towards the cortex to reach completion within a few months after birth (9).

H. W. Smith (15) found that in adults psychic emotions may cause a depression of diodrast clearance, while the filtration rate remains constant, so that a considerable increase in the filtration fraction is seen. This is probably due to a constriction of the vasa efferentia.

We have found that in most infants pain may cause a marked

depression of both PAH and inulin clearances, with an almost constant filtration fraction, suggesting that the depression is brought about by inactivating some of the nephrons by a constriction of the vasa afferentia.

In adults the filtration rate and the PAH clearance do not depend on the diuresis. Dependence of the filtration on the diuresis is, however, seen in adult rabbits (10), and it has been observed in infants by YOUNG & MCCANCE (19) and BARNETT & *al.* (5). The latter found that in one case (an infant with extrophia vesicae) the filtration rate for each kidney varied between 4.4 and 20 ml/min when the diuresis (for one kidney) varied between 0.5 and about 3.5 ml/min (both values corrected to a surface of 1.73 sq. m.).

On the other hand, BARNETT & *al.* (3) state that the filtration rate increases very little with increasing diuresis.

In 23 of our experiments the diuresis was increased (by means of intravenous fluid administration) from about 1.7 ml/min per 1.73 sq. m. to more than five times this value. Only in 9 of these (independent of age and birth weight) was there a correlation between the diuresis and the inulin and PAH clearances, which increased by 50—100 per cent. The filtration fraction remained almost constant in most of these cases, suggesting that the increase in the clearances was brought about by opening the vessels (vasa afferentia) to some nephrons which had been inactive in the periods with low diuresis.

We have not studied the kidney function during dehydration, but MCCANCE (12) has stated that with low diuresis the kidney function will be impaired owing to decreased filtration. It is most probable that the effective renal blood flow will also decrease.

Summary

Inulin and PAH clearances were determined in 55 experiments on infants aged 1—118 days with birth weights from 1100 to 3750 g. In the first week of life the inulin and PAH clearances were 12—14 viz. 50—60 ml per min per 1.73 sq. m. body surface. Both increased rapidly in the following weeks, though with great individual variations. There was no significant difference between

the values obtained from full-term and premature infants with birth weights over 1500 g. Clearances from infants with lower birth weights were rather low, but not definitely outside the normal ranges. The filtration fraction was on an average 0.32.

Both the inulin and PAH clearances were depressed by pain and, in some of the experiments, increased by increased diuresis. In both cases the filtration fraction remained almost constant, suggesting alterations of the number of active nephrons (by variations mainly in the vasa afferentia).

Résumé

Des précipitations d'inuline et de PAH ont été déterminées dans 55 expériences faites sur des enfants âgés de 1—118 jours pesant à la naissance de 1100 à 3750 grammes. Pendant la première semaine d'existence, les précipitations d'inuline et de PAH ont été de 12—14, à savoir de 50—60 ml par minute et par 1 m^2 73 de surface de corps. Toutes les deux ont rapidement augmenté pendant les semaines suivantes, bien que cette augmentation ait présenté de grandes variations individuelles. Il n'y a pas eu de différence significative entre les valeurs obtenues chez les enfants nés à terme et les enfants nés avant terme dont le poids à la naissance dépassait 1500 grammes. Les précipitations chez les enfants de poids inférieur lors de la naissance étaient assez basses, mais pas absolument en dehors des limites normales. Les fractions de filtration étaient en moyenne de 0.32.

Les précipitations d'inuline et de PAH étaient toutes les deux abaissées par la douleur et, dans le cas de quelques unes des expériences, elles étaient augmentées par l'augmentation de diurèse. Dans les deux cas, la fraction de filtration se maintenait presque constante, ce qui semble indiquer des changements du nombre de néphrons actifs (les variations se produisant principalement dans les vasa afferentia).

Zusammenfassung

55 Versuche mit Inulin und PAH Niederschläge wurden bei Kindern in Alter von 1 Tag bis 118 Tage und Geburtsgewicht von 1100 bis 3750 g gemacht. In der ersten Lebenswoche waren

Inulin und PAH Niederschläge 12—14, also 50—60 ml in 1 Minute auf 1.73 Quadratmeter Körperoberfläche. Beide stiegen schnell in den folgenden Wochen an, zwar mit individuellen Variationen. Es bestand kein grosser Unterschied in Verhalten unter den normal ausgetragenen und den Frühgeburten mit Geburtsgewicht über 1500 g. Dagegen bei den Frühgeburten mit kleinerem Geburtsgewicht war der Niederschlag tiefer obwohl nicht ausserhalb normalen Grenzen. Die Filtrationsfraktion war durchschnittlich 0.32.

Beide Inulin und PAH Niederschläge waren heruntergesetzt bei Schmerzen und in manchen Versuchen bei erhöhter Diuresis. Filtrationsfraktion dagegen unter diesen Umständen blieb konstant, vermutlich Veränderungen in der Zahl von aktiven Nephronen (hauptsächlich bei Veränderungen in den Vasa afferentia).

Resumen

Han sido determinadas precipitaciones de inulina y de PAH en 55 experimentos hechos con niños de una edad comprendida entre 1 y 118 días, pesando a su nacimiento de 1 100 a 3 750 gramos. Durante la primera semana de existencia, las precipitaciones de inulina y de PAH han sido de 12 a 14, o sea de 50 a 60 ml. por minuto y per 1.73 m^2 de superficie del cuerpo. Ambas han aumentado rapidamente durante las semanas siguientes, aunque este aumento ha presentado grandes variaciones individuales. No ha habido diferencia significativa entre los valores obtenidos con los niños nacidos a su debido tiempo de gestación y los niños nacidos antes de tiempo y cuyo peso al nacer era superior a 1 500 gramos. Las precipitaciones en los niños de peso inferior al nacer eran también bajas, pero de ninguna manera fuera de los límites normales. Las fracciones de filtración eran por término medio de 0.32.

Las precipitaciones de inulina y de PAH eran ambas rebajadas por el dolor y, en el caso de algunos de los experimentos, aquéllas aumentaban con el aumento de diuresis. En los dos casos, la fracción de filtración se mantenía casi constante, lo que parece indicar cambios del número de nefrones activos (las variaciones se efectuaban principalmente en los vasa afferentia.

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FROM THE CHILDREN'S CLINIC, UNIVERSITV OF HELSINKI, AND THE INSTITUTE OF PHYSIOLOGY, UNIVERSITY OF HELSINKI.

Artificially Induced Local Anoxaemia in the Treatment of Children's Anaemia

by

EVA BONSDORFF and ESTER SELESTE

In organisms suffering from anoxia erythropoiesis stimulating substances are known to be formed. Such a substance was first demonstrated by CARNOT and DEFLANDRE (1906) in the serum of anaemic test animals during the period of regeneration. Later the presence of active substances in organisms exposed to a lowered atmospheric pressure and in patients suffering from anoxia caused by a circulatory insufficiency was stated as well (MÜLLER 1911, GIBELLI 1912, FOERSTER 1924, Yu-TIN 1938, LOESCHKE and SCHWARTZER, 1939, BONSDORFF and JALAVISTO 1948).

Even CARNOT and DEFLANDRE tried to use these active substances »haemopoietins» or »erythropoietins» to treat anaemia. They injected »active» serum into anaemic patients, but in spite of an early rise in the red blood picture, they could not obtain any lasting effect. Since then, according to the literature, no further attempt has been made to use serum from anoxic organisms as anaemia treatment. This may be due to the fact that suitable human serum is not always easily obtained.

The erythropoieteins are, however, brought within the reach of clinical use by the observation that they are present not only in the serum from anoxic organisms, but are formed as well when *blood in vitro* is kept in lowered atmospheric pressure (BORNSDORFF 1948). On the basis of this statement a few anaemic patients at our clinic have been given transfusions of desoxygenated blood (YLPPÖ 1949).

Since erythropoietins are present in blood rendered anoxic either in vivo or in vitro, they should accordingly be formed if the oxygen tension of the venous blood in any part of the body is lowered under some critical level.

In the present paper some cases of children's anaemia treated with induced local anoxaemia will be reported.

Methods

Anoxaemic treatment was given to 9 anaemic children aged from $2\,^1/_2$ months to $3\,^1/_2$ years.

8 children suffered from normo- or hypochromic anaemie, while in 1 child hyperchromic anaemia was stated. Patients 2 and 8 had been given no treatment for anaemia previous to the experiment. All the other children had been treated with iron, liver extracts, folic acid and vitamins, but in spite of the treatment showed only a slight tendency to regeneration. In all cases care was taken to avoid remedies during the experimental period.

Local venous anoxaemia was induced by osttructing the venous circulation in a limb. For the purpose a tourniquet was applied on one thigh and a pressure of 50—60 mm Hg maintained for one hour. In some cases (1, 4 and 5) the treatment was repeated two or three times. The patients' red blood cells, haemoglobin and percentage of reticulocytes were determined on the day when the anoxaemic treatment was given and on the few days following the treatment.

Results

The results of the experiments are presented in Tables 1—9. It will be seen that in most cases the treatment was followed by a marked initial increase in the red cell count, which in some cases was levelled off again in a few days. The blood values of several patients remained, however, at a higher level throughout the experimental period of several weeks or even months. Between the reaction of haemoglobin and red cells some discrepancy was stated, probably due to a different mode of reaction of the erythron in different patients. A marked reticulocytosis was observed in only a few cases. After treatment the general condition of most of the patients improved.

Patient No. 1. H P. ♂, aged 17 months.

Diagnosis: Anaemia normochromica, stated February, 1948.

Blood Status					Previous Treatment
3.9.48	Hgb 63/73	Er 4.07	I 0.90	L 5.800	5.2.–12.10.48 Hepator »Extra», Ferr. redukt.
23.9.48	Hgb 63/74				
12.10.48	Hgb 76/88	Er 3.98	I 1.11	R 0.5 %	6.9.48 20 cc maternal blood im.
»	*tourniquet round thigh*				
13.10.48	Hgb 76/88	Er 4.78	I 0.92	R 3.0 %	
14.10.48	Hgb 76/88	Er 4.08	I 1.08	R 0.8 %	
18.10.48	Hgb 76/88	Er 4.44	I 0.99		
»	*tourniquet round thigh*				
20.10.48	Hgb 76/88	Er 4.58	I 0.96		
3.11.48	Hgb 73/85	Er 4.46	I 0.96		
Control					
12.4.49	Hgb 73/85	Er 4.22	I 1.00	R 2.8 %	
	General condition satisfactory				

Patient No. 2. L. V. ♂, aged 8 1/2 months.

Diagnosis: Eczema pruriginosum allergicum, anaemia hypochromica non medicata. Anaemia stated 21.10. 1948.

Blood Status				
21.10.48	Hgb 59/69	Er 4.44	I 0.77	R 0.8 %
»	*tourniquet round thigh*			
23.10.48	Hgb 73/85	Er 4.98	I 0.85	R 2.6 %
25.10.48	Hgb 82/95	Er 5.36	I 0.89	R 2.4 %
17.11.48	Hgb 82/95	Er 4.84	I 0.98	R 1.6 %
19.11.48	Hgb 82/95	Er 5.24	I 0.91	E 1.6 %
22.11.48	Hgb 82/95	Er 5.34	I 0.89	R 1.6 %
24.11.48	Hgb 84/98	Er 4.68	I 1.05	R 1.4 %
	General condition good.			

Patient No. 3. S. R. ♂, aged 13 months.

Diagnosis: Anaemia hypochromica, stated 2.10. 1948.

Blood Status					Previous Treatment
2.10. 48	Hgb 59/69	Er 4.22	I 0.84		2.10–20.10. 48 Heptomin forte, Ferr. reduct.
20.10. 48	Hgb 61/71	Er 4.90	I 0.72		
21.10. 48	Hgb 64/74	Er 4.82	I 0.77	R 1.2 %	
»	*tourniquet round thigh*				
23.10. 48	Hgb 68/79	Er 5.12	I 0.77	R 1.6 %	
25.10. 48	Hgb 72/84	Er 5.66	I 0.74		
Control					
9.5. 49	Hgb 72/76	Er 4.55	I 0.80	R 0.5 %	
	General condition improved.				

Patient No. 4. G. S. ♂, aged 11 months.

Diagnosis: Anaemia hypochromica, stated 20.8. 1948.

Blood Status					Previous Treatment
20.8. 48	Hgb 50/53	Er 4.200	I 0.60	L 8.400	20.8. 48 Benuton c. strychnin
22.9. 48	Hgb 58/61	Er 3.690	I 0.78		Pentafer, Acid. asc.
24.9. 48	Hgb 77/89	Er 4.760	I 0.94		Devitol forte
3.11. 48	Hgb 60/63	Er 3.580	I 0.79		Caseoferrin
5.11. 48	Hgb 66/77	Er 4.480	I 0.86		22.9. 48 Heptomin forte
8.11. 48	Hgb 66/77	Er 4.440	I 0.87	R 0.8 %	
»	*tourniquet round thigh*				
10.11. 48	Hgb 60/70	Er 4.720	I 0.74	R 1.1 %	
12.11. 48	Hgb 74/86	Er 4.46	I 0.96	R 1.4 %	
»	*tourniquet round thigh*				
14.11. 48	Hgb 84/98	Er 5.24	I 0.93	R 1.4 %	
16.11. 48	Hgb 82/95	Er 4.42	I 1.08	R 1.2 %	
18.11. 48	Hgb 84/98	Er 4.42	I 1.11	R 1.2 %	
25.11. 48	Hgb 76/88	Er 4.24	I 1.03	R 1.3 %	
Control					
9.5. 49	Hgb 63/67	Er 4.02			
	General condition good.				

Patient No. 5. J. R. ♂, aged 25 months.

Diagnosis: Anaemia hypochromica, stated 13.10. 1948.

Blood Status					Previous Treatment
13.10. 48	Hgb 50/53	Er 3.200	I 0.76	R 1.0 %	13.10. 48 Folic acid. 10 amp. Hepator »Extra», Ferr. reduct.
5.11. 48	Hgb 60/64	Er 3.960	I 0.77	R 0.8 %	
3.12. 48	Hgb 62/66	Er 4.390	I 0.73	R 0.4 %	3.12. 48 Heptomin, Devitol forte, Ferr. red. Folic acid.
10.1. 49	Hgb 60/64				
14.1. 49	Hgb 60/70	Er 4.02	I 0.87	R 3.0 %	
»	*tourniquet round thigh*				
15.1. 49	Hgb 71/82	Er 4.12	I 1.00		
16.1. 49	Hgb 78/91	Er 4.62	I 1.00	R 2.9 %	
	experiments stopped because patient contracted measels 18.1. 49				
10.2. 49	Hgb 67/78	Er 3.86	I 1.01	R 2.8 %	
»	*tourniquet round thigh*				
11.2. 49	Hgb 74/86	Er 3.88	I 1.10	R 2.8 %	
12.2 49.	Hgb 76/88	Er 4.02	I 1.10	R 4.0 %	
14.2. 49	Hgb 80/93	Er 4.22	I 1.10		
10.3. 49	Hgb 68/79	Er 4.02	I 0.98	R 3.0 %	
»	*tourniquet round thigh*				
11.3. 49	Hgb 70/81	Er 4.42	I 0.92	R 3.0 %	
12.3. 49	Hgb 77/89	Er 4.08	I 1.09		
13.3. 49	Hgb 77/89	Er 4.04	I 1.10		
Control					
12.4. 49	Hgb 84/98	Er 4.44	I 1.10	R 2.1 %	
	General condition good.				

Patient No. 6. J. A. ♂, aged 13 months.

Diagnosis: Anaemia normochromica, stated 28.2. 1949.

Blood Status					Previous Treatment
28.2. 49	Hgb 56/59	Er 4.60	I 0.61	L 11.500	28.2. 49 Devitol forte
28.3. 49	Hgb 68/72	Er 4.40	I 0.77	L 7.400	4.3. 49 Caseoferrin B c. ars. Heptomin forte
22.4. 49	Hgb 68/72	Er 4.48	I 0.76	L 13.100	
27.4. 49	Hgb 65/76	Er 4.16	I 0.91	R 1.1 %	28.3. 49 Devitol forte
»	*tourniquet round thigh*				
28.4. 49	Hgb 67/78	Er 4.16	I 0.94	R 1.3 %	
29.4. 49	Hgb 69/80	Er 4.44	I 0.90	R 1.2 %	
30.4. 49	Hgb 68/79	Er 4.88	I 0.81	R 1.2 %	
2.5. 49	Hgb 68/79	Er 4.12	I 0.96	R 1.2 %	

Patient No. 7. R. L. ♂, aged 19 months.

Diagnosis: Anaemia levis normochromica, stated May, 1949.

Blood Status					Previous Treatment
9.6. 49	Hgb 64/74	Er 3.64	I 1.01	R 1.1 %	Hepatonicum, Ferroscorbin. stopped 24.5. 49
10.6. 49	*tourniquet round thigh*				
11.6. 49	Hgb 64/74	Er 3.80	I 0.96	R 1.1 %	
13.6. 49	Hgb 64/74	Er 4.38	I 0.84	R 1.2 %	
14.6. 49	Hgb 68/79	Er 3.96	I 1.04	R 1.1 %	
17.6. 49	Hgb 67/78	Er 4.18	I 0.93	R 1.2 %	
29.6. 49	Hgb 69/80	Er 4.52	I 0.89	R 1.8 %	
	General condition good.				

Patient No. 8. J. S. ♂, aged 3 years 8 months.

Diagnosis: Anaemia hypochromica, stated 14.6. 49. No previous treatment given.

Blood Status				
14.6. 49	Hgb 50/58	Er 3.62	I 0.81	R 1.0 %
»	*tourniquet round thigh*			
16.6. 49	Hgb 50/58	Er 3.64	I 0.81	R 1.1 %
17.6. 49	Hgb 58/67	Er 3.86	I 0.87	R 1.3 %
21.6. 49	Hgb 55/64	Er 4.04	I 0.80	
28.6. 49	Hgb 58/67	Er 4.70	I 0.70	R 1.4 %
	General condition satisfactory.			

Patient No. 9. T. L. ♀, aged 2 1/2 months.

Diagnosis: Anaemia hyperchromica, stated May, 1949.

Blood Status					Previous Treatment
14.6. 49	Hgb 58/67	Er 2.84	I 1.17 %	R 1.2 %	Heptomin forte × 2 in middle of May
»	*tourniquet round thigh*				
17.6. 49	Hgb 63/73	Er 3.42	I 1.07	R 2.8 %	
18.6. 49	Hgb 61/71	Er 3.60	I 0.99	R 3.0 %	
28.6. 49	Hgb 62/72	Er 3.24	I 1.11	R 2.3 %	
	General condition good.				

Conclusions

According to the results presented above it seems as if local anoxaemia which leads to the formation of erythropoietins should be of some value in the treatment of children's anaemia. As the effect of a single administration of erythropoietins to a normal organism is known to be very transient (see BONSDORFF and JALAVISTO 1948) the fact that red cell values of anaemic patients remain high for a longer period after the anoxic treatment, should be discussed. On the basis of the present data it would, however, be imprudent to offer any detailed explanation of the lasting effect. Yet it could be presumed that the erythropoietins formed in the anoxic limb represent an exceptionally strong stimulus for the bone marrow. On the other hand, a strong erythropoietic stimulus applied to an anaemic organism in which the primary cause of anaemia (e. g. infection or iron deficiency) no longer exists but which still shows only a poor tendency to regeneration might successfully assist in the restoration of a normal bone marrow function. Naturally, as long as the primary cause of anaemia still exists the treatment cannot be expected to have any favourable effect.

Accordingly, the patients best suited to treatment with erythropoietins would be those in whom no other cause for the anemia than a poor function of the bone marrow can be stated.

Summary

Nine anaemic children were treated with local venous anoxaemia induced by obstructing the venous circulation in a limb for one hour. In most patients the treatment caused an increase in the red blood picture which in some cases lasted for some months and had a favourable effect on the general condition.

Résumé

Neuf enfants anémiques ont été traités par une anoxémie veineuse locale causée en obstruant, pendant une heure, la circulation dans les veines d'un membre. Le traitement a produit,

chez la plupart des patients, un accroissement des globules rouges du sang lequel s'est maintenu quelques mois, dans certains cas, et a eu un effet favorable sur l'état général.

Zusammenfassung

9 anämische Kinder wurden mit lokaler Anoxaemie behandelt. Die venöse Zirkulation an einem Glied wurde für eine Stunde unterbrochen. Nach dieser Behandlung resultiert bei den meisten Patienten eine Zunahme der Zahl der roten Blutkörperchen die ein Paar Monaten andauerte und gleichfalls ein günstiger Einfluss auf den allgemeinen Zustand.

Resumen

Nueve niños anémicos fueron tratados por una anoxemia venosa local provocada por obstrucción de la circulación venosa en un miembro durante una hora. El tratamiento ha ocasionado en la mayor parte de los enfermos un aumento del número de los glóbulos rojos que, en ciertos casos, ha durado algunos meses y ha causado un efecto favorable sobre el estado general del paciente.

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FROM THE CHILDREN'S CLINIC OF THE UNIVERSITY OF HELSINKI.
CHIEF: PROFESSOR A. YLPPÖ.

The Pyruvic Acid (p. u.) Content in the Blood in Congenital Heart Disease

by

C.-E. RÄIHÄ and H. TALLQVIST

Premature and newborn infants show a pronounced acidosis during the first few days of life (YLPPÖ 9) which is regarded as a result of anoxemia in the fetal state (RÄIHÄ 6). The excretion of pyruvic acid into the urine is increased during the first days after birth (RÄIHÄ 7, TALLQVIST 8) and there is also a heightened p. u. concentration in the blood (ALLIBONE 2). In cesarean sections performed on sheep, KARVONEN et al. (4) were able to demonstrate a gradient in the p. u. contents of fetal blood in the direction from the fetus to the mother. The identical gradient is also found in normal human labour (TALLQVIST 8). Persons living on a height of more than 4 000 m above sea level show increased p. u. values in the blood (MONGE 5). It appears therefore that chronic anoxemic states produce an elevation in the p. u. content of the blood. Since children with serious congenital cardiac defects must be regarded as suffering a chronic lack of oxygen, we have deemed it advisable to examine the p. u. in the blood of 5 cases with serious congenital heart disease, predominantly of the tetralogy if Fallot type, who have been hospitalized in the course of this year at the Children's Clinic in Helsingfors.

To make the p. u. analyses we have recurred to the method of FRIEDEMANN and HAUGEN (3). Benzene was used as solvent and 2—4 dinitrophenylhydrazine as colour reagent. The colour was read from a Coleman spectrophotometer at a wavelength of 5 200 Å.

On the basis of his own and earlier investigations, ALLIBONE (1), has assessed the normal p. u. content of the blood of healthy children at an average of 0.78 mg per 100 ccm blood. Our own controls are fully consistent with these values in 3 cases only; in which infants with chronic rheumatoid arthritis were involved. The values obtained by us were somewhat increased (1.5, 1.6 and 2.3 mg per 100 cmm blood). Toxic, infectious and hemolytic states increase the p. u. content of the blood (ALLIBONE 1, 2). The cause is obscure, but it has been proved that thiamine therapy has no reducing influence.

In order to eliminate to the greatest possible extent an increase in the p. u. values induced by infection, the specimens were withdrawn during the last days before the patient's discharge. Case 3, however, constitutes an exception in this respect, the patient having succumbed to acute pneumonia two days after the taking of the sample.

The results are illustrated by the following table.

	Age	mg p. u./ 100 cc blood	Diagnosis
1. H. L.	2 months	8.8	vitium cordis congenita
2. M. H.	6 weeks	6.5	tetralogy of Fallot
3. M. P.	3 months	6.1	id.
4. T. B.	18 months	6.6	id.
5. V. R.	2 years 6 months	4.2	id.

Our theoretical postulates were therefore corroborated to a surprising extent, since we were able to demonstrate a great elevation of the p. u. level in the blood in all cases with congenital heart defects. Perhaps one may interpret these results as indicating that there is a tendency to lower p. u. values at a more advanced age.

Imperfect oxygenation of the blood seems to have induced an increased p. u. content in the blood. It is possible that in these patients, who have had ever since their birth to live without sufficient oxygen, these high p. u. values are a result of an increased capacity for anaerobic metabolism resembling that of fetal life. It is our intention to continue our studies of the problems bearing on these questions.

Summary

The writers have found high pyruvic acid values in the blood of 5 cases with congenital cardiac defects of the type of Fallot's tetralogy (4.2—8.8 mg per 100 ccm blood).

The pyruvic acid analyses were performed according to the method of FRIEDEMANN and HAUGEN with benzene as solvent and 2—4 dinitrophenylhydrazine as colour reagent.

It is claimed that these high values are a result of disorders in the carbohydrate metabolism induced by chronic anoxemia in these patients.

Résumé

Les auteurs ont trouvé de hautes valeurs d'acide pyruvique dans le sang de cinq cas de la tétralogie de Fallot (4.2—8.8 mg par 100 cm^3 de sang).

Les analyses de l'acide pyruvique ont été faites d'après la methode de Friedemann et Haugen, avec la benzol comme dissolvant et 2—4 dinitrophénylhydrazine comme réactif colorant.

On prétend que c'est un résultat des désordres dans le métabolisme des hydrates de carbone causés par l'anoxémie chronique chez ces patients.

Zusammenfassung

Die Autoren fanden im Blute von 5 Fällen von Fallotschen Tetrade erhöhte Werte von Brenztraubensäure (4.2—8.8 mg per 100 ccm Blut).

Diese Analysen wurden nach der Methode von Friedemann und Haugen durchgeführt mit Benzen als Lösungsmittel und 2—4 Dinitrophenylhydrazin als Farbenreagens.

Es wird angenommen, dass es sich bei diesen Patienten um eine durch chronische Anoxämie bedingte Störung in Kohlenhydrat-Stoffwechsel handelt.

Resumen

Los autores han constatado altos valores de ácido pirúvico en la sangre de cinco casos presentando defectos cardíacos con-

génitos del tipo de la tetralogía de Fallot (4.2—8.8 mg por 100 cm³ de sangre).

Los ánalisis del ácido pirúvico se han hecho siguiendo el método de Friedemann y Haugen con benzol como disolvente y 2—4 dinitrofenilhidracina como reactivo colorante.

Hacen constar que esto es consecuencia de desórdenes en el metabolismo de carbohidrato, producidos por una anoxemia crónica en los casos tratados.

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(FROM THE PAEDIATRIC CLINIC, UNIVERSITY OF OSLO, RIKSHOSPITALET, NORWAY. CHIEF: PROFESSOR LEIF SALOMONSEN, M. D.)

Chylothorax in Children

A Contribution to the Elucidation of the Pathogenesis

By

WILHELM BLYSTAD and **HJALMAR WERGELAND**

Chylothorax is a rare lesion in children, and only 1 case has been described previously from Norway (ANTHUN 1942).

Chylous exudate may occur after trauma in which the thoracic duct and the pleura have been injured. BRESCIA was of the opinion, however, that the most frequent cause in children is spontaneous rupture. He indicates that in such cases there must be a congenital defect in the wall of the thoracic duct. An obstruction of the duct, either by external pressure (enlarged mediastinal glands, tumours, aneurysms, pericarditis) or by internal closure (tumour infiltration, thrombosis, inflammation), may also be the cause of chylothorax. The lymph accumulates and rupture or bursting occurs of the vascular wall. The possibility is also suggested of penetration by diapedesis (STAEHELIN).

We shall here record a case of a patient who was hospitalized for her lesion on two occasions in 1948 and 1949 in the University Hospital Paediatric Department. The reproduction of exudate had ceased altogether after the first hospitalization, and the patient had a healthy appearance. A little more than three months after discharge, however, she was readmitted into the department with renewed symptoms. A recurrent course of this disease has not been described previously as far as we have been able to ascertain.

First hospitalization. The patient, a female child, was not quite 2 years old when she was first admitted. She appeared to be healthy and thriving until four days before admission, when she suddenly became

restless, and vomited. Next day she was up and about, but her mother noticed that she was short of breath and easily became tired. She had insignificant cough. Afebrile. The dyspnoea was increasing, and on the fourth day a physician was consulted, whereupon the patient was admitted into the department. The previous history held no information of trauma.

On admission her respiration was strikingly rapid — 60, superficial, though not gasping. Temperature 37.6° C. She had an only slightly exhausted appearance. The right half of the thorax bulged somewhat. Massive dullness from apex to base. The respiratory sound was weakened and of a somewhat wheezing character. No foreign sound. Normal conditions were found over the left half of the thorax. The liver was palpable two fingerbreadths under the right costal arch, and the spleen one fingerbreadth under the left costal arch. The examination otherwise showed normal conditions. The presence of right-sided pleural exudate was verified by x-ray examination. By thoracocentesis was tapped 250 ml of dull, greyish white, somewhat transparent fluid, which when left standing formed a fine clot. Microscopy disclosed a few cells, mostly mononuclear, but no microbes.

After the tapping the patient had an untroubled and brave appearance. Afebrile. Good appetite. The blood count was normal and the sedimentation rate 2 mm. The tuberculin test was negative.

As early as two days after the first tapping, however, she was again dyspnoeic, and another thoracocentesis had to be performed. In the course of the following seven weeks she had to be tapped eight times in all, a total of 4050 ml exudate being evacuated. The turbidity of the exudate gradually increased somewhat, and had the appearance almost of skim milk. This remained unchanged after hard centrifugation. On being left to stand a »cream layer» 2—3 mm thick was formed on the surface. Sudan staining during microscopy disclosed numerous fine drops of fat. Chemical analysis gave the following values:

rest nitrogen	— 21.5 mg %,	24.1 mg %;	
protein	— 4.16 %,	4.38 %;	
fatty acids	— 0.105 %,	0.55 %,	0.13 %;
cholesterol	— 80 mg %,	163 mg %,	90 mg %.

Repeated bacteriological examinations gave negative findings, as was also the case with cultivation on tubercle bacilli. Histological examination did not demonstrate any tumour cells. X-ray examination after tapping gave negative findings. Thoracoscopy was also carried out without revealing anything pathological.

The general condition remained remarkably good, almost unaffected, apart from the time immediately prior to the tapping when she was dyspnoeic and somewhat exhausted.

The condition was considered to be a case of chylothorax. She was put on a diet poor in fat and rich in proteins and vitamins. Thoracocentesis was performed when she seemed to be troubled by her dyspnoea. After each tapping penicillin was instilled in the pleural cavity.

The reproduction of exudate occurred on the two last occasions somewhat more slowly, and after seven weeks ceased totally. The patient had the appearance of being quite well after a short time, and she was discharged after a stay of nine weeks.

Second hospitalization. A little more than three months later the patient was readmitted into the department. In her home she had been under medical care, and had appeared healthy. An x-ray examination 10 days previous to admission demonstrated a little fluid on the right side of the pleural cavity. Three days before admission she again became increasingly dyspnoeic.

On admission she was dyspnoeic, and an enormous rightsided pleural exudate was demonstrated. Otherwise the physical examination gave as previously negative findings. During the following seven weeks thoracocentesis had to be performed 11 times, and a total amount of pleural exudate of between 11 and 12 liters was evacuated. The intervals between the tapping were as short as two to three days.

The appearance and character of the exudate was the same as during the previous hospitalization. Bacteriological examination, including cultivation on tubercle bacilli, gave negative findings. The chemical examination of the exudate showed fat values between 0.075 % and 0.505 %, of protein between 2.37 % and 4.84 %, and for cholesterol between 51 mg % and 101 mg %.

The general condition was good except immediately prior to each tapping. She had a good appetite and was in high spirits. Afebrile. The blood count and the sedimentation rate were normal. As previously she was put on a diet poor in fat and rich in protein.

She lost weight somewhat, however, approximately 800 g. As her condition remained unchanged after seven weeks, she was transferred to Surgical Department A of the University Hospital to establish a permanent suction drainage. It was hoped thereby to encourage formation of adhesions. The suction drainage was ineffective, however, the drain immediately blocking up. In spite of this the reproduction of exudate ceased after the intervention. The patient continued to be controlled in the department for four weeks without any recurrence. She appeared perfectly healthy and was in good condition on discharge. During the four months which have elapsed since the operation the patient has been under medical control, and no recurrence of the disease has occurred.

The diagnosis of chylous exudate was established on the following criteria. —

1. The milky look of the exudate. Centrifuging brought no change in the appearance of the exudate, but when it was left to stand a »layer of cream» collected on the surface.
2. Microscopy demonstrated very finely distributed drops of fat by sudan staining. Some cells, predominantly mononuclear.
3. Chemical analysis frequently disclosed a very high content of fat, 5—6 %. As might be expected the fat concentration varied with the composition of the diet, and could be considerably below 1 % on food poor in fat. The total protein content generally lay somewhat below the concentration in serum, though over 3 %.
4. Negative result of bacteriological examination, nor was there any data on which to base an infectious aetiology.
5. Very rapid reproduction of the exudate after tapping was a common occurrence. In some cases tapping had to be performed daily.

When confronted by a patient with pleural exudate, the most natural, purely routine reaction will generally be to think of an infectious aetiology, and one tries to demonstrate the nature of this. All bacteriological examinations in our patient, however, gave negative result.

The fact that we had a case of ascites chylosus in the clinic a relatively short time previously instigated us very early to consider the possibility that this was also a case of chylous exudate. Most criteria for this diagnosis were present, though the macroscopic appearance of the exudate differed fairly much from that observed in the previous patient. The exudate did not present the typical yellowish white, milky appearance, being greyish and transparent. Chemical analysis showed the fat concentration to be strikingly low. On admission it was 0.1 %, and later increased somewhat with maximum values of a little more than 0.5 %.

The fat content of the chyle is determined by the amount of fat administered through the diet. If this is known, it should be

possible to estimate the average fat concentration of the lymph passing through the thoracic duct. A comparison between the expected fat concentration in the lymph and the fat content of the exudate would be of interest in this connection to give us a chance of determining more closely the nature of the exudate. In the course of the second period of hospitalization of the patient some examinations were carried out for this purpose.

The patient was put on a standard diet, the daily known administration of fat through the separate periods of reproduction being kept constant. The fat was given in the form of milk fat, cod liver oil and peanut oil. The daily ingestion was varied according to the different periods of reproduction, and appears from the following table.

The tapping of the exudate between each period was carried out as completely as possible. X-ray control after tapping did not demonstrate fluid in the pleural cavity.

Determination of the fat content of the exudate was performed after each tapping. These analyses were carried out at the University Hospital Medical Laboratory.

As mentioned previously the calculation of the average concentration in the lymph corresponding to the fat administered can be made only approximately. By the moderate administration of fat in question, almost complete resorption should be anticipated. The general condition of the patient was good, and there was no diarrhoea. The major part of the fat passes into the chyle. It is claimed that a minor part, up to 40 %, may be resorbed directly into the portal blood (STARLING 1940). It has been estimated here that 60 % of the fat administered passes into the chyle.

The total amount of lymph passing through the thoracic duct each 24 hours is estimated somewhat variably, usually at not more than 3 liters per adult individual. DRUMMOND (1935) made similar calculations for an adult individual based on a quantity of 3 liters. The quantity for our patient has been estimated at 1 litre per 24 hours, which has presumably been calculated somewhat high on purpose.

In the following table the concentration in the exudate is compared with the calculated concentration in the chyle, corresponding to the different quantities of administered fat.

It is observed that the fat content in the exudate is remarkably much lower than the expected concentration in chyle according to the administration. It should here also be taken into consideration that the difference is probably still higher, as the con-

Table

The fat concentration in the pleural exudate compared with the amount of fat administered through the diet and the expected average concentration in chyle.

Fat Administered per 24 hs in g	No. of Periods	Average Concentration in Exudate mg %	Calculated Concentration in Chyle mg %	Concentration in Exudate in Chyle %
12	1	75	720	10.4
16	2	298	960	31.0
18	4	213	1 080	19.7
40	1	505	2 400	21.0

centration in the lymph has been calculated somewhat low on purpose.

In the literature some exudates similar to chyle, but with different aetiology, have been described. STAEHELIN (1930) distributes these into two groups: the chyliform exudates and the pseudochylous exudates.

In the *chyliform exudates* the fat is derived from degenerated leucocytes and tumour cells, and is coarser and more irregularly distributed. The protein concentration is lower than in usual chylous exudates, below 3 %.

The *pseudochylous exudates* should contain very little or no fat. It has been considered that the turbidity here is caused by fine drops of protein. The reproduction is slow. The aetiology of these exudates is somewhat vague. As indicated by the name, they are not generally assumed to originate in the chyle. GANDIN has claimed, however, that these exudates are also of chylous origin. He is of the opinion that also here the turbidity is in causal relation to fine drops of fat, which it is difficult to extract with ether.

It was considered that a chyliform exudate could be excluded in this case. The choice seemed to lie between a usual chylous exudate and a pseudochylous exudate. The content of fat seemed to vary to a certain degree, however, with the amount administered through the diet. Together with the many other criteria

this makes it a natural result, after all, to look upon the exudate as being of chylous origin.

The pathogenesis in this case must be stated to be obscure.

Two possibilities have been discussed to explain the low content of fat in the exudate, viz.:

1. a dilution of chyle by a reactive pleural exudate;
2. a filtration mechanism, whereby only a smaller portion of the fat was represented in the transudate.

The former explanation appears rather improbable, however. The essential part of the exudate would then have to be of reactive character. To explain the very rapid reproduction a marked inflammatory process would have had to be present in the pleura, which would then presumably have been noticeable in the character of the exudate and in the general condition of the patient. Further, there are no data in previous publications on which to base the conception that the chyle should have a local irritant effect. Repeated bacteriological examinations of the exudate gave negative findings.

It seems by far most probable that the exudate became manifest by a filtration mechanism. The filter must then have been of such a quality that the proteins in which the disperse phase was relatively shorter passed through in unaltered concentration. The fat found in the chyle as finely distributed drops would be filtrated off to a certain extent.

The investigations naturally do not supply data as to how this filtration mechanism is established. From a theoretical point of view several possibilities may be present.

The most natural explanation is probably that there has been in the first instance primarily impeded outlet for the lymph for some reason. The accumulation has made the valvular system insufficient, and there has occurred retrograde filling with chyle of the delicate lymph vessels in the chest. The increased pressure has caused distension here and injury of the vascular wall with augmented permeability. The thoracic duct has a relatively thin wall, and the pressure in the vessel is low. It might be assumed, therefore, that a compression would occur fairly frequently. It is the experience of the surgeons that ligation of the upper part of the duct as a rule causes no chylothorax. When blocking occurs,

therefore, there usually seem to be sufficient anastomoses to drain the chyle by other routes. Thus, a condition for development of chylothorax by a process of accumulation would seem to be an anomaly of the lymphatic system of the chest, with deficient development of anastomoses.

The assumption that some cases of chylous exudate are formed by oozing of fluid without the presence of any defects or flaws in the vascular wall, is not a new one. STAEHELIN, as mentioned, includes such a mechanism among the pathogenetic possibilities. The investigations of the authors also seem to support such a theory to a marked degree.

The amount of fat in such exudates should depend to a great extent upon the permeability of the vascular wall. When the cases are mild, with small injury of the vascular walls, the exudates formed should be almost free from fat. This seems to explain the production of the previously mentioned pseudochylous exudates, and supports the conception of GANDIN that there is no clear distinction between these and the usual chylous exudates.

When one is confronted by a case of chylothorax, the aetiology and pathogenesis is frequently bound to be obscure, as in this case. There is reason to believe that by correlating the fat concentration of the exudate with the quantity administered, a possibility should exist of deciding whether one is dealing with a case of actual rupture of the thoracic duct, or of an accumulation mechanism. This may be of significance for the treatment to be chosen.

The prognosis in chylothorax is variously estimated by the different authors. MC. ENERY and BRENNEMANN maintain that the majority of cases have a fatal issue. FIELD claims that the prognosis in children is much more favourable than in adults, and gives a rate of mortality of 33 %, which agrees with the results arrived at by BRESCIA. The cause of death may be either directly the primary origin of the lesion or cachexia on account of the great loss in nutrition resulting from the tappings.

The treatment consists mainly in repeated tappings. Some investigators hold that tapping should be carried out frequently

and completely, in this way to stimulate formation of adhesions. This was also the object of the suction drainage which was tried in our patient. This trial, however, was unsuccessful. Other authors hold that tapping should not be carried out until the dyspnoea becomes annoying, in order that the hypertension in the pleural cavity may close the defect. No adequate material seems to exist to make it possible to evaluate which of these two principles gives the best results.

When definite data are present on which to base a traumatic aetiology, results are favourable with ligation of the thoracic duct. When there are data pointing at an accumulation mechanism as causal relation, nothing is achieved, of course, by such an intervention.

The various authors agree that these patients should be treated with a diet rich in proteins. The great loss of albumins by repeated tappings may be difficult to compensate, despite such treatment. During the second period of hospitalization of our patient the albumin concentration in the exudate fell to 2.37 %. A control was carried out, therefore, of the serum proteins, which showed a fall to 4.26 %.

A diet poor in fat has been recommended on the basis of the conception that the amount of chyle would be reduced thereby, and consequently the amount of exudate as well. FLORER and OCHSNER, however, found no reduction of the amount of exudate upon reduction of the fat content of the diet. The investigations of the authors with varying administration of fat also failed to give any positive data for this.

Intravenous infusion of the evacuated exudate was also tried. Two of the 10 cases recorded died from allergic shock, however (FORBES).

Ample administration of the fat-soluble vitamins parenterally is indicated, of course.

Summary

An account is given of a case of recurrent chylothorax in a female child just over 2 years of age, with no known trauma or other demonstrable cause.

A marked disproportion was demonstrated between the content of fat in the exudate and that which might be expected to be present in the chyle with the diet administered to the child. The authors are of the opinion that this may indicate that the exudate was not due to a rupture of the thoracic duct, but had been produced by a process of filtration. The investigations made are considered to support the conception that no clear distinction exists between the chylous and the »pseudochylous» exudate.

By correlation of the fat content of the exudate with the amount of fat administered, a pointer may be obtained as to whether a rupture of the thoracic duct is present or not, which may be of significance to the treatment to be used.

Résumé

On décrit un cas de chylothorax récurrent chez un enfant du sexe féminin, âgée juste d'un peu plus de deux ans, sans trauma connu ou autre cause démontrable.

On a démontré une disproportion sensible entre le contenu de graisse de l'exsudat et celui que l'on aurait pu s'attendre à trouver dans le chyle, étant donné le régime alimentaire auquel l'enfant a été soumise. Les auteurs sont d'avis que cela peut indiquer que l'exsudat n'est pas dû à une rupture du conduit thoracique, mais a été produit par un processus de filtration. On estime que les recherches faites appuient l'opinion qu'il n'y a pas de distinction nette entre l'exsudat chylifère et l'exsudat chyliforme.

Par l'établissement du rapport existant entre le contenu de graisse de l'exsudat et la quantité de graisse administrée, on peut obtenir un indice de la présence ou de la non-présence d'une rupture du conduit thoracique, ce qui peut avoir de l'importance pour le traitement à appliquer.

Zusammenfassung

Ein Bericht über einen Fall von wiederholtem Chylothorax ohne ein bekanntes Trauma oder eine andere nachweisbare Ursache bei einem gerade 2 Jahre alten Mädchen.

Es wurde ein bemerkenswertes Missverhältnis zwischen dem Fettgehalt des Exsudates und dem der zugeführten Nahrung ent-

sprechenden Fettgehalt des Chylus nachgewiesen. Die Autoren sind der Meinung, dies beweise, dass das Exsudat nicht durch Ruptur des Ductus thoracicus, sondern durch einen Filtrationsprozess entstanden sei. Die gemachten Untersuchungen stützen die Annahme, dass kein deutlicher Unterschied zwischen chylösem und »pseudochylösem» Exsudat besteht.

Durch Vergleich des Fettgehaltes des Exsudates mit der zugeführten Fettmenge kann genau festgestellt werden, ob eine Ruptur des Ductus thoracicus vorhanden ist ober nicht, was für die anzuwendende Behandlung von Wichtigkeit sein kann.

Resumen

Se describe un caso de quilotorax recurrente en un niño del sexo femenino, de una edad justamente un poco mayor de los dos años, sin trauma conocido u otra causa demostrable.

Se ha demostrado una desproporción sensible entre el contenido de grasa del exudado y el que se habría podido esperar encontrar en el quilo, dado el régimen alimenticio al cual ha estado sometida la niña. Los autores opinan que esto puede indicar que el exudado no es debido a una rotura del conducto torácico, pero que ha sido producido por un proceso de filtración. Se estima que las investigaciones hechas apoyan la opinión de que no hay distinción concreta entre el exudado quilífero y el exudado quiliforme.

Por el establecimiento de la relación existente entre el contenido de grasa del exudado y la cantidad de grasa administrada, se puede obtener un índice de la presencia o la ausencia de una ruptura del conducto torácico, lo cual puede tener importancia para el tratamiento a aplicar.

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(FROM THE PAEDIATRIC CLINIC OF KAROLINSKA INSTITUTET IN THE NORRTULL HOSPITAL. CHIEF: PROFESSOR A. WALLGREN.)

Congenital Facial Diplegia

By

BO HELLSTRÖM

Facial paralysis is a very common occurrence among the newborn. Usually it is due to birth injuries, but in certain cases it has another origin, a hypo- or aplasia of the seventh cranial nerve nucleus. In these children the facial paralysis is often bilateral and to a large extent combined with involvement of other cranial nerves. Further there may be other congenital lesions.

The first description of congenital facial diplegia was written by VON GRAEFE in 1880. In recent years two large reviews of the subject have appeared, one by HENDERSON in 1939, and the other by DANIS in 1945, both of which include an exhaustive survey of the literature. Other reports of cases have been published during the last years, the most recent by MURPHY and GERMAN, 1947. Their case is the only one hitherto investigated by means of air encephalography. The total number of cases reported in the literature is about 90.

During the last few years 2 cases belonging to this category have been admitted to the Norrtull Hospital. One of these (Case 1) was submitted to a thorough investigation which included air encephalography, electroencephalography and electromyography.

Case 1. Boy born Nov. 12, 1947. Case Record No: 102/48, 583/48. Heredity. — Cousin on mother's side, boy born 1943, had amimia, speech difficulties, syndactylia and bilateral talipes. This cousin in turn had cousin on his father's side with club foot. Maternal aunt had polydactylia. Several cousins died during infancy. An elder brother healthy.

Partus normal according to the case record summary. According to mother child's extremities rather blue during the days following delivery.

Rearing and Development. — While in maternity hospital child had difficulty with sucking and had to be fed with spoon. Later there was also feeding difficulty. Binocular fixation at 1 $^1/_2$ months. Grasped at objects at 3 months. Began to sit up without support at about 9 months. Stood with support from 9 $^1/_2$ months. Babbling from about same period.

Illnesses. — Besides feeding difficulties absolute rigidity of expression from birth. Face always quite free from creases. Unable to smile, but able to laugh till he choked while face absolutely expressionless and the corners of mouth not drawn upwards. No movement of face on crying or screaming, on which occasions eyes half open. Blinked seldom and slowly without fully closing eyelids, which were also not completely closed during sleep. When first admitted to hospital (at 3 months of age) had fully developed convergent strabismus; mother could not give definite information as to how long he had had it. According to mother squint less marked and less constant at 10 months of age.

State on Examination at 10 Months of Age. — Normal height and weight. Rigid facial expression (»masklike facies»). No nasolabial furrows, smooth face without a crease. Bell's phenomenon on blinking. No sign of trophic disturbances on skin of the face. Bilateral epicanthus. Lobe of right ear smaller than the left. Pronounced convergent squint. Fig. 1.

Ophthalmic Consultation. — Vision could not be determined. Refracting media clear. Retina deficient in pigment. Macula and optic disc N. A. D. Probably bilateral paralysis of sixth nerve (Wadensten).

Ear, Nose and Throat Examination. — Tongue somewhat atrophic with sparse fibrillar twitching. On crying soft palate moved normally. No paralysis of throat (Hamberger).

Examination of Cerebrospinal Fluid (cells, albumin, W. R.): normal findings.

Examination of Blood Serum (Sabin's in vitro technique). — Patient: no toxoplasmosis neutralization occurred. Mother: positive, titer 1: 40 = possibly an infection suffered earlier. (Gard).

Radiological Examination. — Epiphyses (10 months): normal development. Skull (10 months): mesocephalic type, somewhat enlarged. Anterior fontanel 4 cm long. Sutures around it open. Cranial bones thin. Grooves in posterior fossa somewhat deepened. Vascular markings normal. Base of skull and sella turcica no pathologic changes.

Air Encephalography (3 months). — No dislocation of ventricular system. Lateral ventricles not dilated or altered in any other way. Third and fourth ventricles similarly normal appearance. Posterior cistern and basal cisterns strikingly wide (Lindgren). Fig. 2.

A B

Fig. 1. Case 1 (10 months old). A. Congenital facial diplegia and bilateral paralysis of sixth cranial nerve. Masklike face, convergent strabismus, epicanthus. B. Same patient crying. Complete lack of expression, mouth half open.

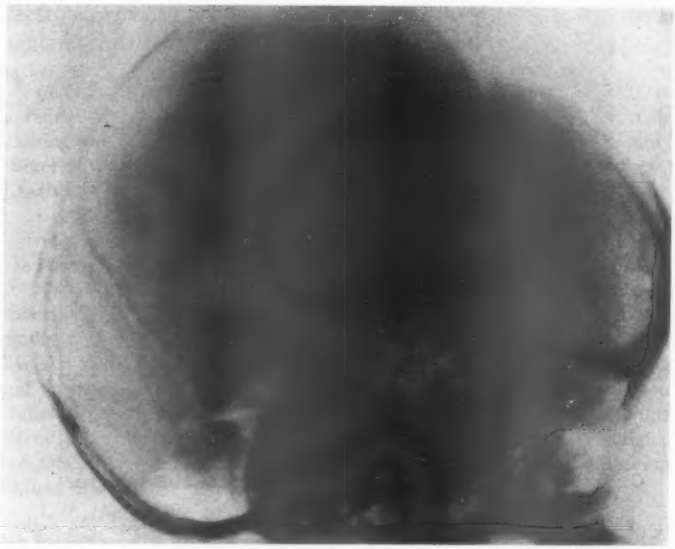
Electroencephalography (10 months). — Dominating frequency 5/sec. From the left anterior quadrant lower amplitude and moderate element of irregular 1—2/sec. activity. Slight element of beta activity, same from both sides. Precentrally periodic 7—8/sec. activity on transverse conduction. Lateral differences might indicate changes in anterior part of left hemisphere. Otherwise curve within bounds of normal variation for corresponding age (E. Holmgren).

Galvanic testing, direct and indirect, of facial area: no reaction.

Electromyography (11 months). — Left corner of mouth: no activity either for mechanical stimulation with needle, spontaneously or on crying. Right corner of mouth: definite voluntary activity. Very scant as very little innervated muscle in existence. Moreover, possibility of some spontaneous fibrillar twitching, conceivably indicating presence to a small extent of denervated or never innervated muscle (E. Kugelberg). Fig. 3.

Intelligent Quotient According to Bühler-Hetzer (10 months): 68.

Summary. — 1 year old boy with feeding difficulties, amimia and convergent strabismus. In heredity history a five year old cousin with similar symptoms. Clinically bilateral paralysis of both superior and inferior branches of facial nerve, bilateral paralysis of sixth cranial nerve and signs that twelfth cranial



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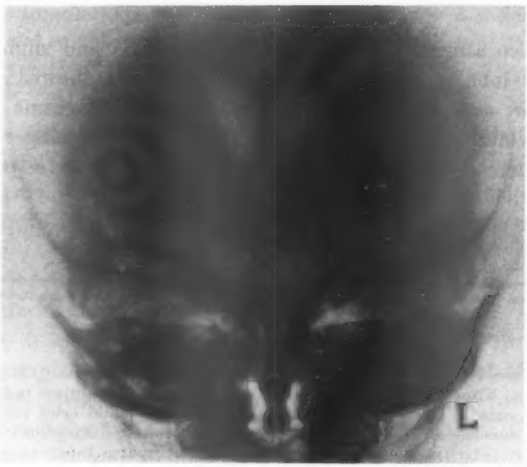

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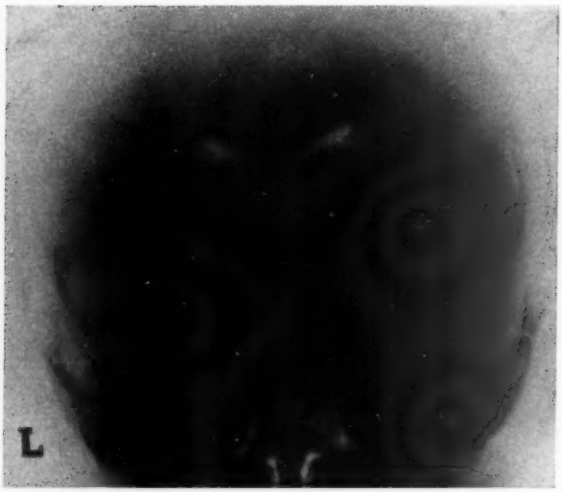

Fig. 2. Case 1 (3 months old). Air encephalogram (LINDGREN). No dislocation of ventricular system. Lateral ventricles not dilated or in any other way altered. Third and fourth ventricles have similar normal appearance. Posterior cisterna and basal cisterns conspicuously wide. A. Side view. B. Front view. C. Back view.

nerve also affected. Bilateral epicanthal folds and slight deformity of lobe of one ear. Air encephalograms showed widened posterior and basal cisterns. Electroencephalograms showed certain lateral differences, possibly indicating changes in left hemisphere. In spite of the apparently complete paralysis,

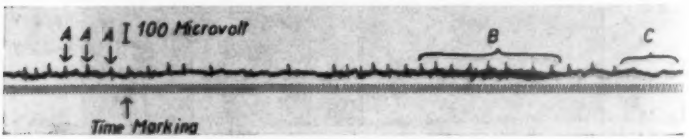

Fig. 3. Case 1 (11 months old). Electromyogram (KUGELBERG). Right corner of mouth. Time markings 1/100 sec. Curve shows an action potential (A) which repeats at fairly regular intervals every time child cries (this appears also on base line, which becomes thickened through microphony (B)). On inspiration activity ceases (C); thus definite but sparse innervation present.

electromyography showed registrable activity corresponding to right inferior branch of facial nerve. I. Q. 68.

Case 2. Boy, born May 23, 1944. Case Record No: 42/47, 332/48. Heredity. — A grandmother's sister had talipes. Partus: N. A. D. Rearing and Development. — From birth difficulty with breast feeding. Therefore child fed with bottle and spoon. Sat without support at 9 months; walked without support at 2 years.

Illnesses. — Mother brought boy to hospital Jan. 1947 because he could not utter a single word. He was thought to understand what was said to him.

State on Examination Jan. 1947. — Gave impression of profound imbecility. Did not speak; uttered only disconnected sounds. Gazed rigidly forward with scarcely any facial expression. Ankyloglossum. Facial paralysis mainly of left inferior branch. Ocular movements up and down normal, but no lateral movements. Phoniatric Consultation. Complete motor inhibition of speech present, undoubtedly due to tongue defect. Tongue fixed to floor of mouth by too short frenum linguae and moreover apparent atrophy of musculature, with fibrillar twitching. Bulbar disturbance? (Kågén)

I. Q. (According to Bühler-Hetzer): 83.

In Feb. 1948 mother reported boy had made great progress both mentally and physically. Could say single words and short sentences, but other people found his speech difficult to understand.

Readmitted for Observation April 1948 (4 years old). — Put short sentences together; speech not clear; spoke with open nasalizing. Left inferior and slight superior facial paralysis. Slight bilateral ptosis. Paralysis of lateral and convergent ocular movements.

I. Q. : 94. With correction for speech difficulties: 101.

Summary. — Four year old boy with partial, probably bilateral, facial paralysis, paralysis of eye movements (lateral and convergent), and slight bilateral ptosis, who, principally on account of speech difficulties, was suspected of being mentally deficient. I. Q. showed normal mental development.

The pathologic-anatomic examination of a few cases of congenital facial diplegia who died (HEUBNER 1900, RAINY and FOWLER 1930 and SPATZ and ULLRICH 1931) has revealed a hypo- or aplasia of the nerve cells in the nucleus of the facial nerve. In 2 cases a macroscopic hypoplasia of the brain stem area around the facial nuclei has also been observed. This is of special interest and might explain why it is possible to establish

the hypoplasia radiologically. Thus MURPHY and GERMAN 1947 have described a case of congenital facial diplegia in which an air encephalogram showed enlargement of the basal cisterns, especially the cisterna pontis, the cisterna interpeduncularis and the cisterna chiasmatica. The distance from the ventral surface of the pons to the floor of the fourth ventricle was smaller than normal. Also in Case 1. described above a similar widening of the basal cisterns could be established.

Concerning the *etiology* opinions differ. Undoubtedly the hereditary factors must be considered to play a part (cf. Case 1). In the sporadic cases the possibility of intrauterine damage to the embryo must be taken into account. From recent investigations it is known that virus infections in the mother in the second and third months of pregnancy can cause multiple malformations in the embryo. The best known is that of rubella (GREGGS 1941). Also, protozoal infections such as toxoplasmosis can cause damage to the embryo which is sometimes reminiscent of hereditary malformations (SABIN 1942). (In Case 1 the mother had a positive toxoplasmos reaction but of a low titer and probably of no importance in regard to the child's disease.)

Symptomatology. — Facial diplegia is usually revealed soon after birth through the child's having great difficulties in sucking and not closing its eyes during sleep. After some weeks or months the mother usually notices that the child cannot smile and that it does not move its face on crying. If other cranial nerves are involved or if there are other deformities, one can infer the congenital cryptogenetic character of the syndrome.

According to HENDERSON bilateral facial paralysis involves all four quadrants (superior and inferior branches bilaterally) in about $^1/_2$ of the cases. The next most frequent is both superior quadrants, while in $^1/_4$ the paralysis involves three quadrants (both superior and one inferior). Only in 1 case were both inferior branches affected with superior branches intact. An interesting fact described for the first time in Case 1 is that a certain activity can be demonstrated by electromyographic examination despite the fact that clinically the paralysis appears to be total.

DANIS has especially studied the symptomatology in his investigation and observed an almost regular occurrence of events; with facial diplegia, for example, hypoglossal paralysis or clubfoot almost never occurs unless there is at the same time a paralysis of the sixth nerve. Cranial nerves other than the facial are involved in 77 % of the cases, of which 64 % are oculomuscular nerves. Especially common are combinations of facial diplegia + paralysis of the sixth cranial nerve. Besides the oculomuscular nerves the hypoglossal nerve is often involved (23 %), while the vagus group of nerves is never affected. DANIS has also studied changes in oculo-motility and points out that in some of the cases, there might be paralysis of conjugated ocular movements, indicating a supranuclear lesion. He has further, like PHILIPSEN-PRAHM 1944, demonstrated a defect in the provoked labyrinthrine functions which points to a lesion of the fasciculus longitudinalis medialis with a breaking of the fibers connecting the vestibular and oculomotor nuclei.

Of the other somatic deformities and defects clubfoot occurs most frequently (30 %). Another group of deformities involve the thorax; aplasias of the ribs, breasts or pectoralis major muscle. Brachial deformities also occur (syndactylia, brachydactylia etc.). Bilateral epicanthus is relatively common. Minor deformities of the external ear can occur (Case 1) but, for some reason, are never so severe as they tend to be in the *unilateral* facial paralyses.

Mental deficiency is demonstrated in about 10 % of the cases. It is generally said, often without foundation, that in infancy and pre-school age the child is grossly mentally deficient (amimia, poor speech ability etc.), which, of course, has important practical consequences. On closer examinations and testing, however, the results are usually surprisingly normal (normal I. Q. in Case 2; 68 in Case 1 at 10 months). The children thus present a pseudoimbecility.

As for the *prognosis*, the condition is, of course, to a great extent unchangeable. In the cases that have been described the observation period has, as a rule, been short. Despite the fact

that the somatic changes are stationary, mentally the child develops at a relatively normal pace.

Summary

An account is given of 2 cases of congenital facial paralysis combined with oculo-muscular paralysis and atrophy of the muscles of the tongue. One of these was thoroughly investigated by, among other methods, air encephalography and electromyography. The air-encephalogram showed a widening of the basal cisterns reflecting a hypoplasia of the brain stem. Electromyography showed partial activity of muscles of expression on one side indicating sparse intact innervation despite the fact that clinically the diplegia appeared complete.

Résumé

On décrit deux cas de paralysie faciale congénitale combinée avec une paralysie oculo-musculaire et une atrophie musculaire linguale. L'un de ces cas a été examiné minutieusement, entre autres, par les méthodes de l'encéphalographie et de l'électromyographie. L'encéphalogramme a montré un élargissement des cisternes de base, qui reflète une hypoplasie du tronc du cerveau. L'électromyographie a montré une activité partielle des muscles mimiques d'un des côtés, indiquant une innervation en petite partie intacte, bien que cliniquement la diplégie ait paru totale.

Zusammenfassung

Ein Bericht über 2 Fälle von kongenitaler Facialislähmung kombiniert mit Augenmuskellähmung und Atrophie der Zungenmuskeln. Einer der Fälle wurde genauest untersucht, unter anderem mit Enzephalografie und Elektromyografie. Das Enzephalogramm zeigte eine Erweiterung der Basalcysterne, zurückzuführen auf Hypoplasie des Hirnstammes. Das Elektromyogramm ergab eine teilweise Aktivität der mimischen Muskulatur der einen Seite, was eine bis auf einen kleinen Teil ungestörte Innervation bewies trotzdem klinisch eine komplette Diplegie vorhanden zu sein schien.

Resumen

Se describen dos casos de parálisis facial congénita combinada con una parálisis óculo-muscular lingual. Uno de los casos ha sido minuciosamente examinado, entre otros, por los métodos de la encefalografía y de la electromiografía. El encefalograma ha mostrado una dilatación de las cisternas de base, que refleja una apoplejía de la base cerebral. La electromiografía ha mostrado una actividad parcial de los músculos mímicos de uno de los lados, indicando una inervación intacta en pequeña parte, aunque clínicamente la diplejía ha aparecido completa. —

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CASE REPORTS

A Case of Ovarian Agenesia

By

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One of the fairly constant signs encountered in the syndrome known as ovarian agenesia, also called Turner's syndrome, is a disturbance of the longitudinal growth which may be evident from birth. Accordingly, the syndrome is of particular interest for pediatrics and for an understanding of the phenomena of growth-disturbance, especially in girls.

In the present paper the case is described of a child suffering from this syndrome, who has been under our treatment for the past two years. The prolonged observation and the results of the different forms of treatment applied during that time, have led to a concept that may deserve some attention, especially in connection with the more recent literature on this syndrome.

The girl X was admitted to the Pediatric Clinic in October 1947, at the age of 14 years. She was the younger of two children of healthy parents. The elder child, a 16-year-old boy, was healthy. The reason for admission to the Clinic was retardation of growth and a suspicion that this had some relation to the syndrome of ovarian agenesia. The girl's parents showed normal development, as do (or did) the grandparents. Diseases found among the relatives were diabetes and cholelithiasis. The family's social circumstances were favourable. When pregnant with our patient the mother did not exhibit any particular disturbances; lactation was satisfactory.

The patient was born spontaneously, at full term, in Indonesia. She cried immediately. Weight at birth 2 500 g. Breast feeding for two months, then diluted cow's milk. She showed poor growth; as a baby she vomited a great deal. In due course she received vitamins and additional feeding. Dentition, sitting, walking, and talking started at the appropriate times. Ankylostomiasis at the age of 4, whooping cough at 5, measles at 6, tonsillotomy at 7. After a hookworm cure at the age of 4 the patient's appetite increased considerably, and the vomiting ceased. At the age of 6 she came to Holland. She has always been very timid. When she went to school for the first time she was so undersized as to attract attention. During the past year she has been growing in breadth, especially in the shoulder region and the pelvis. For about five months she had been taking a thyroid preparation, the result being a decrease in body weight. At the same time she had become gayer

and more active. She was still childlike in her behaviour, preferring to play with girls her junior by many years. There was as yet no question of secondary sex characters or of menstruation. Very moderate learning ability. The appetite was good and she slept well. Micturition and defaecation: nothing of importance.

Condition at the time of admission:

Short, broad girl, rather thick-set (fig. 1), dark skin. Height 132 cm (as compared with normal 157 cm), weight 35 kg (normal 48.2 kg). Shoulders high and with a slight forward tendency. Dark, heavy, stiff hair. Pulse and respiration normal. Sinciput narrowing slightly towards the front; flat occiput. Left rima palpebrarum somewhat slanting. Slight convergent strabismus; minor ptosis; eyes opened well. Scleral region around the iris unusually blue owing to strong pigmentation of underlying strata which shine through (Dr. ROELOFS). Large auricles; absence of lobes of the ear. Right nasolabial fold somewhat slackened. On movement of the mouth, the lower margin of the right cheek in particular lagged slightly behind (slight facial paresis). Teeth of the lower jaw very narrow. High palate. Short neck; pterygium colli; further no particular features.

Fig. 1.

Thorax wide with sunken sternum. Slight kyphosis in the upper thoracic portion of the vertebral column. Slight scapulae alatae. Very small nipple with strong pigmentation of the areola papillaris. No mammary glands palpable. No axillary hair. Heart and lungs: nothing of importance. Abdomen: no pubic hair. Liver and spleen not enlarged. Pulsations of the femoral artery clearly palpable. External genitals (Dr. VAN DONGEN) normal. Introitus narrow but still within normal limits. Portio palpable. Uterus small, in accordance with age. Extremities: pronounced mobility of the joints of fingers and wrist. Fingers slightly flattened. Feet in valgus position with hallux valgus. Great toe unusually short, second and third toe also short. Large spread between first and second toe. Reflexes normal.

Urine: no anomalies in routine examination. Creatine and creatinine excretion: creatine excretion relatively increased. Morphological blood

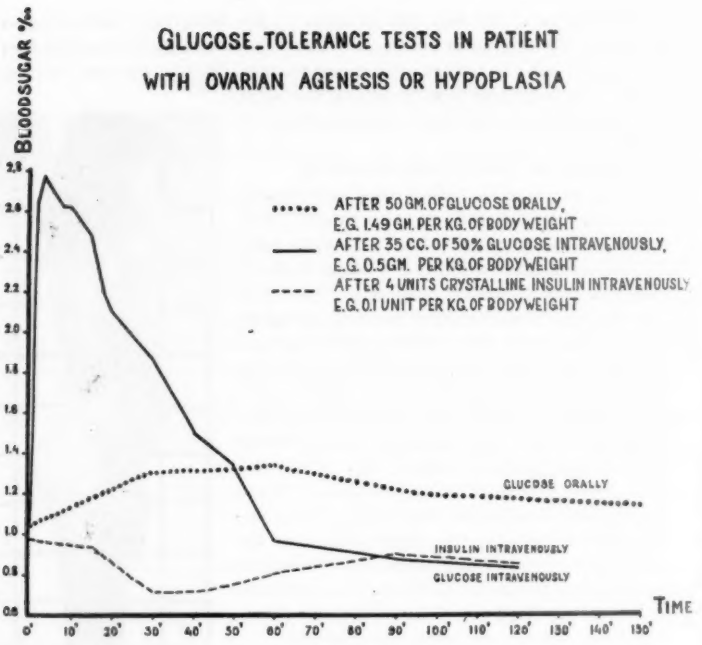
GLUCOSE-TOLERANCE TESTS IN PATIENT
WITH OVARIAN AGENESIS OR HYPOPLASIA
BLOODSUGAR %
AFTER 50 GM. OF GLUCOSE ORALLY, E.G. 1.49 GM. PER KG. OF BODY WEIGHT
AFTER 35 CC. OF 50% GLUCOSE INTRAVENOUSLY, E.G. 0.5 GM. PER KG. OF BODY WEIGHT
AFTER 4 UNITS CRYSTALLINE INSULIN INTRAVENOUSLY E.G. 0.1 UNIT PER KG. OF BODY WEIGHT
GLUCOSE ORALLY
INSULIN INTRAVENOUSLY
GLUCOSE INTRAVENOUSLY
TIME
0' 10' 20' 30' 40' 50' 60' 70' 80' 90' 100' 110' 120' 130' 140' 150'

Fig. 2.

examination: no particular data. Tuberculin tests and serological tests for syphilis negative. Kidneys: dilution and concentration normal. Basal metabolism +7.6 %. Blood pressure 100/70 in the arms, 125/95 in the legs. Blood: calcium, phosphorus, phosphatase (units), sodium, potassium, urea and cholesterol all normal. Blood sugar fasting, normal; blood sugar curve after 50 g of glucose rather flat (fig. 2). Intravenous blood sugar curve after injection of 35 ml of 50 % glucose (0.5 g/kg) normal. Blood sugar curve after 0.1 U. of crystalline insulin per kg (intravenously) normal. (Crystalline insulin kindly supplied by Dr. E. DINGEMANSE.) Binet-Simon test more or less in accordance with age.

Roentgenograms of the skeleton: osteoporosis, especially in pelvis, extremities and hands. Mediastinum rather broad. Digital impressions rather marked. Sella turcica normal. Carpal skeleton fully developed, except the pisiform bone which was still absent.

The roentgenogram of the vertebral column (fig. 3) showed a picture closely resembling Scheuermann's kyphosis adolescentium. In connec-

Fig. 3.

tion with this X-ray finding Dr. La Chapelle cooperated in examining the patient. In his opinion the anomaly was due to a defect in the apophysis of the vertebrae. There was no question of a plate (accordingly no epiphysis), but only of a ring not participating in the growth of the vertebrae. At the age of about 20 this apophysis should be solid and at the age of 25, closure should be complete. The apophyses remain open in various conditions, including myxoedema. In our patient it must be assumed either that ossification of the apophyses had entirely failed to occur in certain vertebrae or that it was not yet sufficiently advanced. These are things that time alone will show. It was found that the patient's kyphosis could still be corrected successfully (lying

flat during the night and avoiding strenuous gymnastics). Slight scoliosis was also observed. The roentgenogram further showed the existence of a spina bifida occulta in the fifth lumbal and first sacral vertebrae and the fact that on the right the normal sacralisation had proceeded slightly farther than on the left. Moreover, the epiphyseal discs were still open, but the patient was at an age of transition in this respect. Thanks to the treatment recommended by LA CHAPELLE an X-ray of the vertebral column taken three months later already showed some amelioration.

Hormones in urine[1]:

Gonadotropic substances per 24 hours:
1st time 80 I.U.,
2nd time 100 I.U.,
17-ketosteroids 2.8 mg per litre.

On the basis of the results obtained in the physical and laboratory examinations we concluded that the patients syndrome was very similar to, if not identical with, the cases that have been described during recent years as ovarian agenesia or hyperplasia and that her growth disturbance was in some way related to the latter. In those cases, as in our patient, there were other congenital anomalies besides the disturbance of growth. In accordance with our view of the case, the girl was treated exclusively with oestrogenic compounds.

From October 25th, 1947, she received 0.5 mg of stilboestrol daily for two weeks, then from November 8th, 1 mg daily. On October 13th she had swollen ankles, and from December 15th to December 18th slight vaginal bleeding for the first time! The use of stilboestrol was discontinued on December 15th. In the urine from December 21st—22nd 60 U. of gonadotropic hormone were again found.

December 22nd: height 135 cm. Incipient formation of mammary tissue, areolae mammae more pigmented, axillary and pubic hair still absent. Stilboestrol treatment was started again from January 1st, 1948, the doses being from January 1st to January 15th 1 mg daily; after January 15th 0.1 mg daily for the time being. From January 19th to January 24th vaginal bleeding occurred for the second time. On January 19th stilboestrol treatment was discontinued. The areolae mammae showed slightly increased pigmentation. From January 27th to February 10th 1 mg of stilboestrol daily. From February 11th to February 18th 0.1 mg of stilboestrol daily. The urine of January 26th—27th contained 100 U. of gonadotropin. From February 19th to February 24th renewed

[1] Our grateful acknowledgements are due to Dr. DINGEMANSE for performing this examination.

bleeding (i.e., somewhat earlier). From March 1st stilboestrol was again administered: the first week 1 mg daily, than 0.1 mg daily for two weeks; the fourth week nothing. Bleeding re-appeared on March 16th, lasting until March 19th. Administration of stilboestrol was discontinued on March 16th; from March 18th to April 5th, stilboestrol was given again in doses of 0.1 mg daily.

After this period we waited to see whether menstruation would appear spontaneously without administration of stilboestrol. On May 3rd, this had not yet occurred. From May 3rd onward stilboestrol was given again in doses of 1 mg daily and (after one week), 0.1 mg daily. On May 28th there was still no bleeding. On May 31st it was decided to administer stilboestrol again in order to stimulate vaginal bleeding. From June 20th to July 1st the patient received 0.5 mg twice a day, from July 1st to July 7th 1 mg twice a day orally. On July 14th a bleeding occurred.

On continuing this treatment we met with objections on the part of the patient, who tolerated the stilboestrol poorly (nausea) and refused to go on taking the tablets. Ethinyl oestradiol (lynoral) in doses of 25 to 50 mg per day orally was also poorly tolerated.

On August 29th it was agreed to give oestradiol benzoate in oil, 50 000 I.U. daily (5 mg), three times a week for six weeks. The total number of injections given amounted to 20. On October 21st, a few days after the final injection, there occurred a rather violent vaginal bleeding, lasting for five days. From then on no treatment was given until the middle of November; during that time there was no spontaneous bleeding.

As there had been no trace of hair growth until then, it was decided to institute a treatment with testosterone propionate, for the time being 5 mg daily for six days a week, while at the same time 10 drops of dimenformon was administered sublingually t.i.d. This was continued until February 1st, 1949. The result was increasing hair growth of the face (upper lip), slight axillary, and marked pubic hair growth. No bleedings, however, were observed during that period.

It was decided to continue testosterone therapy, while substituting oestradiol benzoate intramuscularly for the dimenformon drops. A mixture of 20 mg of testosterone propionate and 5 mg of oestradiol benzoate in 1 ml of cod liver oil was prepared. With this preparation the patient was injected three times a week for periods of three weeks alternating with one week pause. This resulted in the patient having a vaginal bleeding regularly each interval, while towards the end of May 1949 the condition of the secondary sex characters was as follows (see fig. 4): there was a marked development of the mammae and pigmentation of the areolae; marked pubic and moderate axillary hair growth. The longitudinal growth continued slowly and regularly. According to the

parents, the general condition was better than ever before. It seemed highly indicated, therefore, that the therapy of androgen-oestrogen association should be continued, taking into consideration the results of roentgenological examination of the skeleton, especially in connection with the tendency of the epiphyseal disc to become closed under the influence of androgens.

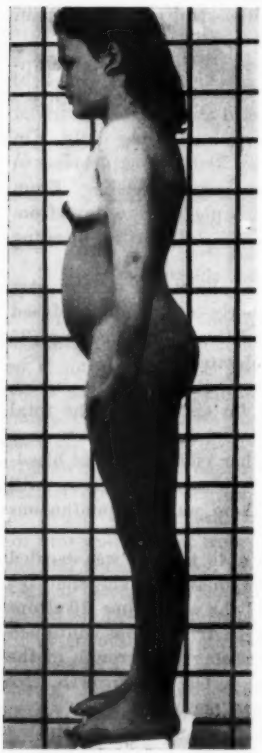

Fig. 4.

Various manifestations of similar cases in children have previously been described as independent syndromes. The question was whether among the phenomena observed there were any that pointed to ovarian agenesia. This was occasionally the case. Dr. M. DE BRUIN, for instance, in his publication on congenital pterygium colli, cited the case reported in 1902 by FUNKE. In this case a 15-year-old girl showed no development of either mammae or nipples, there was no hair on the armpits or mons veneris, and menstruation had not started.

In 1938 TURNER observed 10 cases in women, characterised by retardation in longitudinal growth and sexual development, as well as by pterygium colli and cubitus valgus. The fact that in these cases there was usually congenital aplasia of the ovaries, was not recognised until a few years later.

In 1942 VARNEY, KENYON, and KOCH described four undersized women, backward in sexual development, all of whom excreted abnormally large amounts of gonadotropins in the urine. On the basis of seven autopsy reports found scattered throughout the literature, the authors assumed that aplasia of the ovaries was one of the cardinal features of the syndrome presented by their patients.

In the same year ALBRIGHT, SMITH, and FRASER described 11 similar cases, emphasizing above all the importance of a primary insufficiency of the ovaries for this syndrome, as distinguished from primary hypophyseal infantilism. Two of the patients had been examined with the peritoneoscope on which occasion no ovaries could be seen.

In 1944 SHERESHEVSKI reported six cases with manifestations of such a nature as to invite the conclusion that they should certainly be placed

in the same category, although the author himself did not consider the possibility of absence of the ovaries. The elimination of gonadotropins was not determined either.

Since 1944, complete absence of ovarian development has been demonstrated more than once by means of biopsy.

We became acquainted with the syndrome through a verbal communication by Dr. L. WILKINS, endocrinologist in the Pediatric Clinic of the Johns Hopkins Hospital, on the occasion of a visit to Baltimore. In 1944 WILKINS and his co-worker, W. FLEISCHMANN, described three cases of this syndrome in children and gave a survey of other cases reported up to that time. The latter amounted to a total of 18 cases in which autopsy or laparotomy showed either absence or rudimentary development of the ovaries. The syndrome was termed »ovarian agenesis» by WILKINS and FLEISCHMANN.

Of late two important papers on the syndrome have been published. First DEL CASTILLO, DE LA BALZE, and ARGONZ reported 8 cases and then LISSER, CURTIS, ESCAMILLA and GOLDBERG 25 cases.

It is safe to say, therefore, on the basis of fairly wide experience, that the syndrome is marked by either congenital aplasia or complete absence of the ovaries, sexual infantilism and excessive urinary excretion of gonadotropins, although there are exceptions to this rule (DORFF and co-workers); moreover, the patient usually shows retardation in longitudinal growth. The latter, however, as is apparent from the communication by DEL CASTILLO and co-workers, needs not always be present. Further, there are frequently other congenital anomalies such as congenital pterygium colli, cubitus valgus and not infrequently coarctation of the aorta.

In all, more than 90 cases have been reported so far, in which the diagnosis has either been proved or may be assumed on the basis of the clinical picture. Various names have been given to the syndrome: »Turner's syndrome», »ovarian agenesis» (WILKINS and FLEISCHMANN), »syndrome of rudimentary ovaries with oestrogenic insufficiency and increase in gonadotropins» (DEL CASTILLO and co-workers), »congenitally aplastic ovaries, etc.» (LISSER and co-workers), and others.

The retardation in growth, if any, was noted in early life; the combination of retardation in growth and delayed sexual development, on the other hand, usually did not become apparent until much later. The patients often have a thick-set habitus, the thorax being enlarged both frontal and dorsal and broader than normally. There is usually only sparse pubic hair, while the axillary hair is either absent or equally sparse. Occasionally a patient with constitutional hirsutism was seen. As a rule the external genitals are infantile. The adnexa uteri were never palpable. Some cases showed a low blood pressure, others hypertension. The latter, however, was not limited to the upper portion of

the body and did not necessarily indicate the existence of a coarctation of the aorta. Besides the above-mentioned congenital anomalies the following were occasionally found: haemangiomatosis of the intestinal wall giving rise to grave intestinal haemorrhage, Madelung's deformity of the wrist, osteogenesis imperfecta tarda (osteopsathyrosis), abnormal position of a toe, spina bifida occulta and abnormal development of the skeleton.

Of great importance in this syndrome is the differential diagnosis from primary hypophyseal infantilism in which there is also delayed growth and disturbed sexual development. As an essential point of difference we may mention that in hypophyseal infantilism the excretion of gonadotropins in the urine is slight or zero; in aplasia or hypoplasia of the ovaries, on the other hand, there is increased urinary excretion of gonadotropins. Other points of difference between congenital aplasia of the ovaries and hypophyseal dwarfism are listed below (compare DEL CASTILLO c. s.).

Congenital aplasia of the ovaries.	*Hypophysiary dwarfism.*
1. Patient usually undersized.	Dwarfism.
2. Usually scanty hair growth in armpits and pubic region, increasing after oestrogen therapy.	No hair growth in armpits and pubic region, not even after administration of oestrogens.
3. Rather solidly built skeleton with broad, deep thorax.	Delicately built skeleton.
4. Skeletal development either corresponding to age or slightly backward.	Skeletal development severely delayed.
5. Excretion of 17-ketosteroids decreased to a greater or less extent.	Highly decreased excretion of 17-ketosteroids.
6. Frequent coexistence of other anomalies such as coarctation of the aorta, pterygium colli, and cubitus valgus.	Absence of these anomalies.
7. Delayed closure of the epiphyses.	Complete absence of closure of the epiphyses.
8. Normal intravenous glucose and insulin curves.	Curves show lag.
9. Often extensive osteoporosis.	No osteoporosis.
10. Sella turcica normal.	Sella turcica often pathological.

As said before, therapy during the first year of the treatment consisted exclusively in administration of stilboestrol orally or oestradiol benzoate by injection. With relatively small amounts of stilboestrol a with-

drawal bleeding could be obtained regularly. Development of the mammae started from the very beginning of treatment and has continued ever since. The vulva was never severely hypoplastic, so that its development had not been very marked.

Some authors give other programmes and dosages of oestrogen therapy (LISSER and co-workers), but as far as we know this type of therapy is practically the only one mentioned in the literature. Any treatment with gonadotropic preparations is obviously senseless, while androgens are usually considered inadvisable.

When, however, even after an intensive treatment with oestradiol benzoate no trace of axillary or pubic hair was found, the question arose whether it might not be necessary to give some androgenic compound (testosterone propionate) in addition to oestrogens. If certain cases of ovarian agenesia may be viewed as an expression of developmental disturbance involving not only the ovary but the entire steroid system, i. e. also the adrenal cortex, such a double substitution is certainly preferable. In this connection the reader is referred to the article by one of the present authors (DE VAAL) and especially to an autopsy report on a case of ovarian agenesia with complete absence of axillary and pubic hair, in which there were found, in addition to underdeveloped ovaries, very small adrenal glands with normal medulla but severely hypoplastic adrenal cortex (ATRIA and co-workers).

On the subject of combined oestrogen-androgen therapy it may be remarked that the oestrogen component counterbalances the ovarian deficiency; in other words, it stimulates the female gonadal puberal manifestations. The androgen component, on the other hand, provides a substitute for the deficient androgenic adrenal cortex, thus stimulating the female adrenal puberal manifestations. The latter include (in girls) the appearance of axillary hair, to some extent also the pubic hair and possibly also the puberal growth.

According to some investigators, including ALBRIGHT, the lack of axillary hair and of the full development of pubic hair in ovarian agenesia may have a functional basis. According to this view, stimulation of the androgenic adrenal cortex by the hypophyseal L.H. factor may be obtained by administration of oestrogens, as in this way the F.S.H. factor is inhibited and the L.H. factor is released. Thus administration of oestrogenic substances will give rise to the appearance of axillary and pubic hair.

As in our patient the manifestations of adrenal puberty appeared promptly after treatment with testosterone, whereas intensive oestrogen therapy had failed to produce this effect, we are compelled to assume that in her case there was no such functional basis, but rather there existed some fundamental anatomical anomaly of the adrenal cortex (chiefly of the androgenic zone).

As to the aetiology we are still in the dark. Generally, an embryonal lesion is assumed. In view of the progress made in the knowledge of the causes of evolutionary disturbances (vitamin and other deficiences, diseases during pregnancy) prudence is called for here.

Familial occurrence of the syndrome has not been described up to now; the patients may have perfectly normal brothers and sisters. Ovarian agenesia should perhaps be regarded as an extreme stage of gonadal intersexuality, in which the sexual tubes may have been formed normally (sometimes ovarian rests resembling adrenocortical tissue). Sometimes gonadal sex intergrades also show a high gonadotropic urinary titre.

Summary: Attention is drawn to the syndrome of ovarian agenesia, characterized by disturbance in growth, osteoporosis and enlarged excretion of gonadotropic substances in the urine; next to these symptoms various other ones may be present. Description of a case in a girl, 14 years old, treated with a combined oestrogen-androgen therapy.

Note at the correction

Since this article was written we could observe a girl of 5 years old showing a complex of symptoms present in cases of ovarian agenesia (stunted growth, webbed neck, coarctation of the aorta). The determination of the urinary hormone excretion (dr. DINGEMANSE) learned that the excretion of estrogenic substances was very small as is physiological at this age. In correspondence there was no enlarged excretion of gonadotropins such as is typical for the disease after puberty has been reached. The insulin curve was normal. No deviations of the sella turcica on the X-ray.

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Severe Myocardial Damage in Chronic Atrophic Arthritis

By

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The presence of an association between acute rheumatic infection and chronic atrophic arthritis has been much debated and has been denied by the majority of workers. The reasons for this, inter alia, are the divergences between the clinical picture and the course of disease of the two conditions. That cases do occur, however, in which the differential diagnosis initially is impossible to determine is exemplified by the following case.

Case report: E. L., b. 16/6 1941. KLB No. 129/47.

The case is that of a girl aged 8 who for more than 2 years has been treated at Kronprinsessan Lovisa's Children's Hospital for a chronic joint disease with grave cardiac changes.

Hereditarily the father earlier when working as a coachman suffered much discomfort from "Rheumatic pain".

Of *children's diseases* the patient has had mumps, measles, whooping cough and chicken-pox, the latter in 1943. Because of incessant colds and coryza abrasio was performed in 1946. She has with these exceptions been healthy until the onset of the present disease.

The *present disease* debuted in September 1946 with fatigability, loss of appetite, weight loss, and pain in her joints, at first especially in the knees. There was no preceding disease with fever, no throat infection and no cough. Towards the end of November she had a sudden onset of chills and a high temperature and was admitted to a local hospital where she was treated for 2 months under the diagnosis: Endocarditis?. She there received penicillin in several installments but as she did not show any response to the treatment she was in February 1947 referred to Kronprinsessan Lovisa's Children's Hospital.

Her general condition on admission (weight 19.8 kg, height 119 cm) was very poor with acute dyspnea but with absence of cyanosis. She

complained of pain in the right knee and the left elbow. Examination of the *joints* showed some thickening of the capsule medially over the right knee but no reduction of the passive mobility. There was in both elbows an expension defect of about 15° but no thickening of the capsule or swelling of the joints. The remainder of the joints were normal. There were isolated small crepitant rales over the lungs. The liver and spleen were not palpable. The *heart* was markedly enlarged, the left margin in the anterior axillary line and the right margin somewhat outside the right sternal edge. There were observed pulsations in jugulum and over ictus. The sounds were weak, clear but with an accentuated and doubled second sound over the pulmonary orifice. No friction rub. Rhythm regular. Tachycardia (157 beats per min.). Blood pressure 100/75. X-ray revealed a pronounced cardiac enlargement with absence of signs of pericarditis and stasis of the pulmonary fields with a narrow pleural coat marginally on both sides. ECG showed signs of myocardial damage (prolonged AV conduction, lowered ST segments). The initial complexes were normal. S. R. 101 mm/1 hr. Antistreptolysin titer (AS) 160 units per ml. Blood culture negative. Urinanalysis: Albumin 0. Glucose 0. Blood status: Hgl 62%. Red cells 3.5 millions. White cells 9600 with a slight shift to the left.

The patient received large doses of penicillin intramuscularly, first 25,000 O. U. (Oxford units) × 8 and subsequently 40,000 O. U. × 8, and also digitalis (Cedilanid 5 drops × 3). The treatment had no immediate effect on the general condition and the high temperature (39° C). A period of medication with sulfa preparations in addition did not give any improvement either. After 2 weeks of penicillin therapy there appeared urticaria which was allayed by Antistine, $^1/_2$ tablet × 3, notwithstanding a continued penicillin medication. After 2 months of penicillin treatment without improvement of the temperature 5% Na-salicylate was set in, 1 dessert spoon × 4, this after the interval of about a week being followed by a fall of the temperature to subfebrile values, but without any noteworthy effect on the joint discomfort. After 2 further months of treatment the temperature became normal.

In August 1947 after 6 months of uninterrupted penicillin treatment and 4 months of salicylate treatment all medication was withdrawn and the patient remained afebrile. She then had only slight joint symptoms but still had dyspnea on the slightest exertion. During this period the heart showed a successive decrease in size and the signs of pulmonary stasis had completely disappeared. The ECG still showed signs of myocarditis. The S. R. had fallen from 101 to about 40 and AS was between 200 and 300 units per ml.

During the next 2 months there was continuous improvement. The only treatment was exercise and massage of the joints. The patient was ambulatory. In October 1947 there was a recidivation with fever and for

the first time, *pain in the finger joints* in which there was established a slight diffuse swelling, especially on the right side. No reduction of mobility. No roentgenologic nor electrocardiographic deterioration of the heart, but still a definite cardiac enlargement. After 2 months of penicillin and salicylate therapy she again became afebrile and was in a fairly good general condition.

During the first 6 months of 1948 her condition was largely stationary with the exception of a couple of short exacerbations with a rise of temperature, increased dyspnea and subjective descomfort from various joints. At the nape of the neck there were palpated subcutaneous nodes and there was enlargement of the lymph glands of the neck, the axillae and the inguinals. Penicillin, salicylates and digitalis were administered periodically. Heart X-ray and ECG status unaltered. S. R. 30—40 mm. During a summer sojourn in her home her appetite was very poor and she was re-admitted in October 1948, mainly because of a weight loss of 2 kg. She now had increased discomfort from the large joints (knees, elbows) as well as from the small finger joints. Axillae and hips, however, were at no period affected. The joint status showed a tendency towards ankylosis with reduction of movement in extreme positions and tenderness on movement of the large joints of the extremities and of the joints of the fingers. Over the interphalangeal joints of both hands, and particularly of the index and the third finger, there was present a certain thickening of the capsule. The nodes at the nape of the neck had increased in size, now ranging in size from pea to hazel-nut; they were firm, non-tender, free towards the skin but partially adherent to the underlying tissue. Biopsi of a small node gave a histological picture of normal lymph node without allergic changes or signs suggesting rheumatic granuloma. There was a slight polyadenitis. The spleen was not palpable. The heart status was unaltered.

The condition of disease has since then progressed slowly and insidiously. Her general condition is poorer and her weight stubbornly remains at 17 $^1/_2$ kg notwithstanding all attempts to improve it by feeding her up. Height 119 cm. The joint changes have gradually progressed with increasing stiffness and thickening of the capsules of the small finger joints and the joints of the feet, in spite of continuous massage and exercise therapy. The cardiac changes are stationary on the X-ray as on the ECG. S. R. still about 40 mm.

Conclusions: The case is that of a now 8-year-old girl with a joint and heart disease, in which the onset occurred with joint symptoms in September 1946 and which 3 months later became acutely deteriorated with a high temperature and signs of severe myocarditis. As penicillin had no effect she was referred to Kronprinsessan Lovisa's Children's Hospital. She was very ill on admission with a high temperature, acute dyspnea and tender joints (knees, elbows) with some reduction of mobility. The

small joints were at that period not affected. The heart was markedly enlarged but with absence of murmers. No certain signs of pericarditis. ECG showed grave myocardial changes. S. R. 101. AS normal. Blood culture negative. She was treated with penicillin, digitalis and salicylates over prolonged periods. During the 2 years since admission there has gradually developed a chronic condition dominated by changes of the joints with pain, thickening of the capsules and reduction of mobility of the large as well as now especially the small joints. There is also cardiac enlargement with absence of an objectively demonstable valvular heart disease but with apparently serious stationary myocardial changes on the ECG. There is also present fatigability, lack of appetite, tendency towards dyspnea, polyadenitis and subcutaneous nodes in the occiput.

Discussion: The onset of the symptoms in the present case, thus especially the extreme cardiac enlargement which dominates the clinical picture, is in very good agreement with the clinical picture of a subacute rheumatic infection with severe myocarditis. The further course with the gradual development of pronounced chronic joint changes and the absence of chronic valvular heart disease shows that there in this case probably initially was present a chronic atrophic arthritis in which the myocardial lesions were unusually marked. Because of this feature the case to a certain extent combines the acute rheumatic infection and the chronic atrophic arthritis. Not until the etiology of the rheumatic diseases has definitely been cleared up, however, will it be possible to follow a potential association between the acute and the chronic rheumatic disease.

Summary

The chronic atrophic arthritis and the acute rheumatic infection commonly show clinical pictures clearly divergent with regard to symptomatology and course. A case is described in which the clinical symptoms at the onset were in closer agreement with the acute form but in which there gradually developed a chronic atrophic arthritis with uncommonly marked myocardial changes.

Myasthenia Gravis of a Newborn Child

By

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Myasthenia gravis is a very rare disease among children. In the literature 35 cases of children under 17 years of age are described and of these only 8 were under 8 years. Only in 1 case was a newborn child reported to have myasthenia gravis (WILSON and STONER 1944). This child was born of a 25 year old woman who had had myasthenia gravis for about one year. At birth the child showed typical symptoms of the disease: it did not cry, made very weak movements with the tongue, sucked and swallowed very poorly and often regurgitated milk through the nose. Other symptoms were very weak movements of the legs and arms, poor respiration and occasional cyanosis. Gradually the condition became better and after five weeks the child was completely normal. When a check was made three years later nothing abnormal worth mentioning could be found.

At the pediatric clinic of Lund a similar case has recently been treated.

432/49. Bengt S., born April 26, 1949. The child's mother has myasthenia gravis. Otherwise there have been no noteworthy sicknesses in the family. He has a sister born in 1932, who is well. She was born before the mother developed symptoms of myasthenia gravis. These began in 1936 and took the form of difficulty in speaking and swallowing. Gradually the symptoms progressed and it was necessary to increase the doses of prostigmine constantly. In 1938 she managed well with one tablet of prostigmine twice a day. In 1945 she reached a dosage of 1.5 mg of prostigmine subcutaneously eight—ten times daily together with a tablet of ephedrine (0.025 g) three times daily. Gradually the dosage of prostigmine was increased to 1.5 mg subcutaneously at one and one-quarter hour intervals during the day and three—four times during the night. The thymus was removed in 1946 (thymus persistens) and she could thereafter be managed with a prostigmine injection every third hour. The patient still has, however, constant difficulties in talking and swallowing, finds it hard to walk and can sit only for a short while.

In 1948 she became pregnant with expected delivery on May 26, 1949. The labor pains began on the morning of April 26, the membranes ruptured in the afternoon the same day and the child was born 18 hours after the labor pains began.

At birth the child weighed 3 190 g. He was strikingly limp, cried

weakly and experienced noticeable difficulty in ridding himself of phlegm in the throat. He was immediately transferred to the pediatric clinic. During the next days the picture did not change. He lay completely still in bed with considerably decreased tonus in the legs and arms. He lacked the strength to cry at all and could not suck. His respiration was poor and he gradually became cyanotic. His internal organs did not show anything noteworthy. The blood value and the differential count were normal. X-ray showed no signs of an expansive process in the region of the thymus.

When myasthenia gravis was suspected prostigmine was injected 0.1—0.15 mg three—four times daily. A while after the injection respiration was improved and cyanosis disappeared. The child cried weakly but the tonus was still considerably reduced and the ability to suck or swallow was still lacking. Therefore forcible feeding was begun. Generally speaking the condition was unchanged during the first weeks. Thereafter the child began to swallow so that after three weeks we could discontinue the forcible feeding and administer the food with a spoon. Approximately simultaneously the breathing improved. The child cried properly, moved his arms and legs spontaneously and had a significantly improved tonus. At 1 month of age the prostigmine was discontinued and when the child was discharged at the age of 5 weeks there were no signs whatsoever of any sickness. The weight upon discharge was 3 900 g.

Discussion

There are different theories about the etiology of myasthenia gravis.

1. The cholinesterase activity at the myoneural junction is abnormal and does not permit the normal action of acetylcholine.
2. The amount of acetylcholine liberated at the myoneural junction is less than normal.
3. Some by-product of acetylcholin prevents the normal action of acetylcholin, or some »curare-like» substance blocks the receptor mechanism with a similar effect.

In 1944, WILSON and STONER made a very thorough pharmacological and clinical investigation of 14 cases of myasthenia gravis. They showed clearly that the serum cholinesterase activity in patients with myasthenia gravis was not increased. They demonstrated in the blood of these patients a substance partially soluble in alcohol which in some way blocked the myoneural transmission. Prostigmine should act as an antagonist to this substance. Compare the clinical similarity between curare poisoning and myasthenia gravis and the known antagonistic action between curare and prostigmine.

Two theories may be proposed as an explanation of our case.

1. This case was a true hereditary myasthenia gravis and the improvement to virtual freedom from symptoms which took place was a spontaneous remission in the course of the sickness.

The fact that myasthenia gravis is not considered a hereditary sickness speaks against this theory. It is true that we have the previously described case of a newborn child showing the symptoms of myasthenia gravis where the mother also had myasthenia gravis. The child, however, became free of symptoms after five weeks and was still well after three years. If the child really had had the sickness one would have expected some symptoms to develop during this time.

2. During its prenatal life the child is influenced by the mother's blood and that substance in the blood which causes her clinical condition is transferred to the child. In the child it causes a typical case of myasthenia gravis. After birth it takes a couple of weeks before the child disposes of this substance.

This latter explanation seems the more probable, but only the subsequent development of the child can give a definite answer to the question.[1] One wonders, however, why children of mothers with myasthenia gravis only very seldom show the symptoms of the disease.

If, however, the latter theory is correct, it is very important to try by all means to carry the child through the first critical weeks. The greatest difficulty is to give it enough nourishment, since it cannot suck or swallow. Forcible feeding must be used and in our case we repeatedly gave the child small amounts of concentrated food (citric acid milk). Additional fluid was administered subcutaneously during the first days. There is a large risk of aspiration and pneumonia since the patient lacks the ability to swallow or cough. Penicillin should be given prophylactically. It is of value to use oxygen if the respiration is poor and the child cyanotic. Prostigmine should be given. In our case we gave 0.10—0.15 mg four times daily, with fair but significant effect.

Summary

1. A case of a newborn child with myasthenia gravis whose mother also had myasthenia gravis is described. One similar case has been found in the literature.
2. After five weeks the symptoms disappeared.
3. The theory is advanced that a substance which causes the mother's disease is transmitted during intrauterine life to the child producing the picture of myasthenia gravis. It takes several weeks after birth

[1] The child is still seven months old quite well.

for the child to free itself of this substance, whereupon the symptoms of myasthenia gravis disappear.

4. The importance of extremely careful hospital treatment during the first weeks is emphasized.

Reference

WILSON, A., and STONER, H. B.: Quart. J. Med. 1941, 13, 1.

Myeloblastic leukaemia

By

BENT MØLLER

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Cases of myeloblastic leukaemia are often described on account of the considerable variation in their clinical appearance. In 1943 O. Brandberg (2) tabulated the occurence of the different symptoms in children from a large number of Swedish cases. In the following paper an account is given of 2 unusual and quite different cases. The progress and treatment of the patients gives rise to various theoretical considerations which it is hoped will be found to be of interest.

Case 1 (Case Record 622/47). A boy 3 years old admitted April 14, 1947, in a condition suggesting "internal heamorrhage".

Case History. No family predisposition to blood diseases. Formerly in good health. At the end of January 1947 the patient cought a cold and was in bed for eight days. Thereafter he suffered from weakness and pallor. At the end of March he fell downstairs and hurt his left foot. No ecchymoses were seen, and x-ray examination revealed no abnormality. He was kept at rest for three weeks, during which time his general condition deteriorated and he suffered from excitement, irritability and anorexia. For three days before his admission to hospital he was coughing and febrile.

On admission the patient appeared acutely ill, toxaemic and extremely anaemic. Temp. 39.4° C (102.9° F), pulse 140. No jaundice and no purpura were visible; there was likewise no affection of the mucous membranes of the mouth or throat and no enlargement of the lymph nodes. Respiratory system: pneumonia on the left side. Cardiovascular system normal. Abdomen: large, with considerably enlarged liver and spleen, both extending 2 cm below the costal margin. Genitals: small hydrocele testis. Extremities: normal.

Table I.

Blood examinations from Case 1.

	15/4	27/5	11/6	14/6	19/6
Haemoglobin (100 %=13.8 g)....	27 %	90 %	95 %	90 %	55 %
Erythrocytes (in millions)	—	—	5.25	4.81	3.28
Reticulocytes	0	—	—	—	—
Leucocytes, total	1 400	7 800	13 840	46 000	128 000
Myeloblasts	0	0	0	1	62.5
Promyelocytes	0	1	0	2	1
Myelocytes	0	0	3	6	0.5
Metamyelocytes.....	0	8	17	10	11
Polymorphonuclear Neutrophils..	0	48	46	20	9.5
Polymorphonuclear Eosinophils..	0	1	0	0	0
Polymorphonuclear Basophils ...	0	2	0	0	0
Lymphocytes	77	28	21	27	15.5
Monocytes	33	12	5	3	0
Smudge Cells	0	0	8	31	0
Thrombocytes	4 260	240 000	—	144 000	—
Bleeding Time.....	6 min.	4½ min.	—	—	—
Coagulation Time	6 min.	3 min.	—	—	—
Sedimentation Rate pr. hour....	90 mm	7 mm	—	5 mm	—

Special Examinations. Height 104 cm. Weight 18.1 kg. State of blood: see Table I. Blood group B. Wasserman reaction negative. Tuberculin test negative. Plasma colour (Meulengracht) 4. Urine: albumen 0, sugar 0, nothing abnormal on microscopy. B. P. 125/85. Test meal (Ewald) normal.

Progress. For treatment and state of blood see Table I and Diagram I. On admission the patient was given a blood transfusion of 200 cc Group B into the tibia. We were unsuccessful in aspirating bone marrow on all attempts at tibial puncture. On account of the fever and the leucopenia penicillin was given between April 14 and May 3, a total of 2 015 000 units.

At first the patient was severely anaemic (Hgb. $< 30\,\%$). In spite of repeated transfusions and penicillin, to which we later added injectable liver extract and folic acid, he remained toxaemic. Bone marrow taken from the right calcaneum on April 23 showed panhaematopenia. The composition of this marrow will be mentioned later on.

Sixteen—eighteen days after admission a remarkable clinical improvement took place. The enlargement of the spleen and liver disappeared completely. At the same time the number of erythrocytes, leucocytes

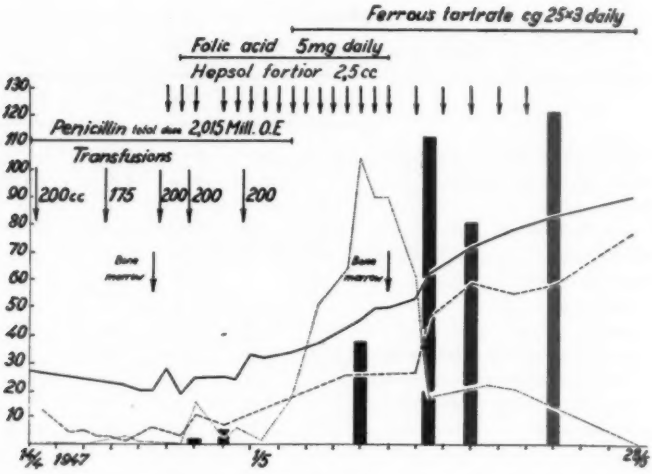

Diagram I.

Haemoglobin in % ———— Reticulocytes in ‰ - - - - - -
Leucocytes in 100 ····· Trombocytes in 2 000 ▮

and thrombocytes increased with equal rapidity and approached their normal values (see Diagram I). There was also a transitory increase in the reticulocytes to 102 ‰. The bone marrow now showed intense regeneration of both erythropoiesis and leucopoiesis. Apart from a slight discolouration of the scrotum no signs of purpura were to be found. The lymph nodes in the neck and groins were slightly enlarged. On May 27, after 43 days, the patient was discharged in good health with a normal blood picture (see Table 1).

For a week after his discharge the patient felt perfectly well, but from then on he suffered from pains in the right arm. He complained of anorexia and constipation, and there was a transitory erythema on the extremities. Upon examination in the Outpatient Department on June 11 his general condition did not seem to be affected and his nutritional state was above normal, but small firm lymph nodes were found on the neck, in the axillae, and in the groins, and the spleen was palpable 2 cm below the costal margin. For the blood picture see Table 1. On the following days the patient was more irritable and in spite of his red cheeks and well nourished condition had no appetite. The circumference of the abdomen increased rapidly and the patient complained of pain there.

On June 14 he was readmitted to hospital. He was mildly ill, with a temperature of 37.7° C (99.9° F). The liver and spleen, however, had increased enormously and reached the umbilicus. The abdomen was distended, with dilated veins in the epigastrium. On both volar surfaces an uncharacteristic erythema was found. The remaining clinical investigation showed no abnormalities; in particular the mucous membranes of the mouth and throat were normal.

Special Examinations. Weight 20.5 kg. State of blood: see Table 1. Urine: albumen +, urobilin +.

Progress. The condition remained almost unchanged until five days after admission, when puncture of the spleen and of the right calcaneum was performed. A few hours after this the patient became acutely ill and died suddenly with an appearance of internal haemorrhage. Blood examinations were made just before death — June 19 — see Table 1.

Autopsy. About 500 cc of partly coagulated blood was found in the peritoneum. The spleen weighed 690 g and was extraordinarily friable with a scratch 2 $^1/_2$ cm long after puncture; small subcapsularly white infiltrations were to be seen. Two accesory spleens 3 cm and 1 cm long were found. The liver, weight 2000 g, was very firm, somewhat tough and light; there were numerous pale infiltrations of 5—10 mm subcapsularly and on the cut surface. The kidneys were enlarged (the right measured 10 × 7 × 3 $^1/_2$ cm, the left 11 × 7 × 4 cm), pale and firm, with dissiminated infiltrations 1 cm long. Infiltrations were also found in the pericardium, particularly perivascularly. The lymph nodes by the bifurcation and in the radix mesenterii were 5—10 mm long, firm and pale on the cut surface. There were no petecchiae subserously or in the parenchyma. The heart, the lungs, the intestinal tract, the pancreas and the adrenals showed no abnormalities macroscopically beyond changes due to anaemia.

Bone marrow. Differential counts of smears from the bone marrow of the calcaneum were made in the aplastic state (April 23), at the time when the regeneration was at its best (May 9), and just before the patient died (June 19). The following distribution was found.

	23/4	9/5	19/6
Myeloblasts	1.00	4.50	98.75 %
Promyelocytes	0	0.75	0
Neutrophil Myelocytes	1.00	6.50	0
Eosinophil Myelocytes	0	0	0
Basophil Myelocytes	0	0	0
Metamyelocytes	8.00	6.00	0
Polymorphonuclear Neutrophils	2.00	4.00	0.50
Polymorphonuclear Eosinophils	0	0	0.25

	23/4	9/5	19/6
Polymorphonuclear Basophils	0	0	0
Lymphoblasts	0	0	0
Lymphocytes	88.00	78.00	0.50
Monocytes	0	0	0
Plasma Cells	0	0	0
Megakaryocytes	0	0	0
Reticulum Cells	0	0.25	0

By counting 400 cells of the white system we found:

Proerythroblasts	4	1
Erythroblasts, Early	113	1
Erythroblasts, Late	227	3

On histological examination of the liver, the spleen, the accessory spleens, the lymph nodes and the myocardium we found large primitive myeloblastic cells everywhere, partly infiltrating, partly in small nodes.

Discussion. As far as we know, no cases have been described which are analogous to this. Kurt Palmen (15) published in 1943 an account of a case of aplastic anaemia in which acute myeloblastic leukaemia developed after clinical recovery. Palmen succeeded in finding 10 similar cases in the paediatric literature, but in none was examination of the bone marrow made either in the aplastic phase or in the remission. Thus "aplasia" has been proved only in the peripheral blood. Such aplastic anaemias are quite often seen during the course of leukaemia (3, 8, 9, 10, 12, 13, 14, 18), and may be explained either as a result of toxic injury to the bone marrow or simply by the fact that active bone marrow is displaced by myeloblasts (11). In the cases described by Palmen the clinical remissions are against this.

Beside the 10 cases he describes I have succeeded in finding 11 apparently similar cases in the literature of the last 10 years, but in only 3 of them were bone marrow examinations performed. These cases are of some interest, and are here summarized.

I (M. P. Dustin, Jr. (4)). A boy 3 years old, badly nourished, developed two severe anaemic crises with leukopenia and thrombocytopenia. After treatment with liver extract complete remission occurred, and primitive leukocytes appeared in the peripheral blood. A third leukopenic crisis swiftly passed into myeloblastic leukaemia. A comparison of the myeolograms from the three successive phases rules out the assumption that a cryptoleukaemia was present in the first two.

II (P. Emile-Weil and S. Perles (6)). A man of 35 who had been exposed for 12 years to benzene vapour developed purpura with anaemia, leukopenia and thrombopenia due to an acute infection (anthrax). No immature cells were found in the peripheral blood, but more than

40 % stem cells were found in the marrow. The myeloblastic infiltration of the bone marrow increased, and 27 % myeloblasts appeared in the peripheral blood. After one week the patient died of "septicaemia".

III. (P. Emile-Weil and I. Perisson (5)). A woman of 53 who suffered from coliuria treated herself for a year with repeated doses of "rubiazol", a sulfonamide. Purpura developed together with ulceration of the mucous membranes. Blood examination revealed anaemia and granulocytopenia. The sternal marrow contained 48 % "elements blastiques" and primitive cells appeared in the blood. After six weeks the patient died from severe anaemia and pneumonia.

In Case I the author supposes the aplasia to have been caused by a break in the maturation, perhaps provoked by undernourishment. It is very interesting to see that benzene, which is used carcinogenically, may provoke total aplasia of the bone marrow or leukaemia preceded by an aplastic phase. It is also remarkable that a sulfonamide, chemically related to benzene and also capable of producing severe granulocytopenia, seems in the third case to have provoked myeloblastic leukaemia.

We think the course of our case may be explained by a general insufficiency of the bone marrow — a disturbance of the maturation — which affected all three of its elements. This disturbance might have been caused by an infectious or toxic state. After the primary or secondary infection had been controlled by penicillin and the state of health improved at the same time by means of blood transfusions, an active regeneration occurred, therapeutically supported by injectable liver extracts, iron and folic acid. In view of the normal blood picture on discharge and the normal regenerative myelogram just mentioned, we deduced the existence of some disturbance of the maturation, with the more confidence since the first bone marrow examination revealed no leukaemia. The transitory enlargement of the liver and spleen might perhaps be taken as a symptom of a transitory extramedullary haematopoiesis, or as a consequence of the patient's "infected" condition.

With a panhaematopenia like that found in our patient, the sepsis accompanying the granulocytopenia will be the most important complication. Perhaps the treatment with antibiotics will result in more frequent observation of "myelophthises" passing into myeloses (10). No doubt our patient would have died in the aplastic phase from sepsis without penicillin treatment.

Case 2 (Case Record 594/47). A boy 14 years old admitted May 3, 1947, for observation of arachnoiditis.

Case History. No family predisposition to blood diseases. Formerly in good health. Six weeks before admission the patient sustained a slight contusion of the left knee, which was tender for a time. Two weeks be-

fore admission he had a slight cough, after which he complained of paraesthesiae and decreased mobility of the lower lip, together with unusual sensations in the masseter muscles. Five days before admission diplopia and strabismus developed, and at the same time spontaneous ecchymoses appeared on the left arm. The highest temperature before admission was 37.8° C (100° F).

On admission his general condition did not seem to be affected. Temp. 37.9° C (100.2° F), pulse 104, nutrition average. Two pale ecchymoses were visible on the left arm, but there were otherwise no signs of purpura. Examination of the eyes revealed diplopia and slight convergent strabismus of the right eye. The pupils were normal and ophthalmoscopy showed normal conditions; in particular there were no retinal haemorrhages. The lower lip perhaps moved less than normal, and slight hyperaesthesia was found to correspond with this. Further neurological examination revealed no abnormalities. No affection of the mucous membranes of the mouth or throat was visible. Respiratory system normal. Cardiovascular system: soft systolic murmur, no further abnormalities. Abdomen: normal, with no enlargement of liver or spleen. The day after admission slight ptosis of the right eyelid was found; in addition there was a green discolouration over the right orbit, and ecchymoses appeared on both legs.

Special Examinations. Height 163 cm, weight 46.5 kg. B. P. 130/85. Hgb. 76 %; erythrocytes 5.19 mill; osmotic resistance 0.56—0.32 %; reticulocytes 5 ‰; leukocytes 17 480. Differential count: 66 % large monocytic cells, including smudge cells, 23 % lymphocytes, 1 % promyelocytes, 3 % rod-shaped nuclear granulocytes, 7 % polymorphonuclear granulocytes, and counting 100 leukocytes, 6 erythroblasts were found, the erythrocytes showing slight aniso- and poikilocytosis. Thrombocytes 51 000. Bleeding time 11 $^1/_2$ minutes, coagulation time 4 $^1/_2$ min., capillary fragility test (Bexelius) showed 54 petecchiae, prothrombin time normal. Plasma colour (Meulengracht) 5, sedimentation rate 30 mm per hour. Blood group 0. Wasserman reaction 12, Kahn negative, Meinicke negative. Antistreptolytic titer 64 (normal). Bunnell negative. Tuberculine test negative. Urine: no albumen, sugar, pus or urobilin; a few erythrocytes were found microscopically. Faeces + + blood. Electrocardiogram: no abnormalities. X-ray of the skull: no abnormalities. On sternal puncture very little bone marrow was aspirated, containing 91 % myeloblasts.

Progress. The main features of the treatment and blood picture are to be seen from Diagram II. The patient was treated with injectable liver extract (Hepsol fortior 5 cc i. m. daily), folic acid and blood transfusions (400 cc blood group 0 every third or fourth day). As the temperature slowly increased he was treated with penicillin at the rate of 200 000

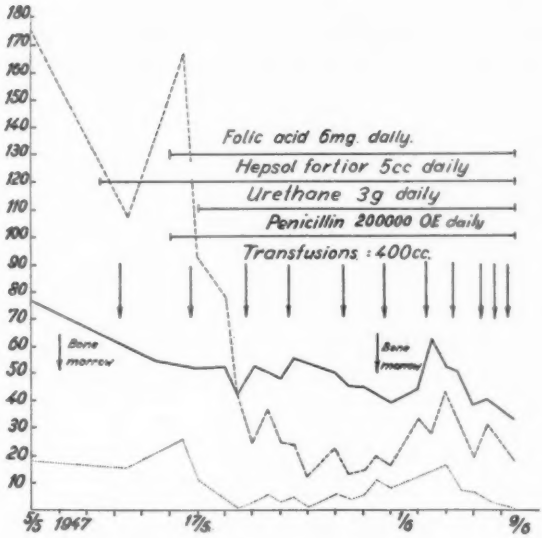

Diagram II.

Haemoglobin in % ———— Leucocytes in 100 - - - - - -
Granulocytes in 100 .....

units daily. On May 17 urethane treatment was started with the following mixture: urethane 40 g, aqua menthae piperitae 600 g; dose 15 cc × 3 daily, corresponding to 3 g urethane. Even before starting this treatment with urethane the leucocyte count was decreasing, and from May 21 until the patient died it was between 1200 and 4000. A transitory decrease in the granulocyte count was followed by an increase to 56%. At that time the sternal marrow contained only 69% myeloblasts. Beside the increase in the granulocyte count we thought we noticed a slight clinical improvement, but the condition varied, and the patient was given many transfusions. Toxaemia and purpura became more and more dominant, the thrombocyte count being between 10 000 and 60 000. Haemorrhages of the retina occurred, and the patient suffered from severe haemorrhagic diarrhoea. In spite of the transfusions acute anaemia ensued which terminated in death on June 10 only 37 days after admission and only 50 days from the onset of the symptoms. No autopsy was performed.

Bone Marrow. Differential counts of smears from the bone marrow were made just after admission and at the time when the differentiation in the peripheral blood was at its best; the following distribution was found.

	7/5	30/5
Myeloblasts	91.25	68.75
Promyelocytes	2.25	0.75
Neutrophil Myelocytes	2.00	1.00
Eosinophil Myelocytes	1.50	0
Basophil Myelocytes	0	0
Metamyelocytes	1.25	3.00
Polymorphonuclear Neutrophils	0	8.25
Polymorphonuclear Eosinophils	0	0
Polymorphonuclear Basophils	0	0
Lymphoblasts	0	0
Lymphocytes	1.75	18.00
Monocytes	0	0
Plasma Cells	0	0.25
Megakaryocytes	0	0
Reticulum Cells	0	0

Among 400 cells of the white system were found:

Proerythroblasts	0	0
Erythroblasts, Early	7	0
Erythroblasts, Late	7	2

On May 7 the bone marrow contained a few megakaryocytes, but three weeks later none was to be found. The sample taken on May 30, however, contained a quantity of peripheral blood, so the increased differentiation and the more pronounced diminution of the erythroblastic cells may be a sign of this "contamination".

Discussion. Many descriptions of the urethane treatment of acute myeloblastic leukaemia have so far been published (16, 17, 19), and its effect seems to be extraordinarily variable. Paterson, for instance, records that in 1 case it led to an improvement, in 1 had no effect and in 2 aggravated the disease. In the treatment of experimental myeloblastic leukaemia in mice it had no effect on the survival of the animals, although the local tumour and the infiltrations were found to be less marked in mice treated with urethane as compared with controls.

In spite of this experience we consider that the treatment is still worth trying, the more so since no other can be offered to patients suffering from acute myeloblastic leukaemia apart from merely palliative measures such as transfusions, chemotherapy and antibiotics. X-rays

seem to be of no value except in cases where there is pressure from enlarged lymph nodes (1, 9). They may, however, aggravate the condition (9). Radioactive phosphorus may also act deleteriously (1).

We think it of theoretical interest that our patient showed greater differentiation both in the bone marrow and in the peripheral blood. It is our opinion that too much importance is generally attached to the blood in assessing the results of the treatment, as the changes in the blood need not inevitably take place simultaneously with the changes in the bone marrow (11). This seems the more important because it is impossible to make use of examinations of the basal metabolic rate in the most febrile acute leukaemia.

In the case of our patient it can hardly be asserted that the urethane treatment had a beneficial effect on the clinical condition since the progress of the case was complicated by our other measures and the severe purpura; we can not be sure that the big doses, of urethane did not damage the thrombopoiesis further. It must also be admitted that the changes in the bone marrow may merely be a sign of the damage to the myeloblasts, not the result of more normal conditions. Our present technique of examination of the bone marrow does not permit the determination of the real amount of its different elements.

Conclusion. At the present time leukaemia is generally believed to be neoplastic in origin. The cases described by Emile-Weil and Perisson, Emile-Weil and Perles and by M. P. Dustin, as well as my own Case 1, where leukaemia developed after panhaematopaenia produced by a carcinogenic substance or by unknown factors, may also support the neoplastic theory, although the nature of the changes in the cells is quite unknown. Perhaps the cell lesions have the primary character of a disturbance in the maturation. In view of this, treatment should include liver extracts, folic acid, vitamins and iron, as in our Case 1. Later, when cell changes are apparently neoplastic, the usual treatment with radiation or anticarcinogenic substances may prove to have some palliative effect, as in our Case 2. With regard to the condition described, where an aplastic bone marrow developed a leukaemic one, it must be mentioned that leukaemia may have the primary effect only of inducing focal changes (7). Thus the existence of an aplastic marrow does not necessarily preclude the possibility of a simultaneous leukaemia (3).

Summary. Two cases of acute myeloblastic leukaemia are described and discussed.

1. A boy aged 3 developed a panmyelophthisis of unknown aetiology (verified by bone marrow examination), severe anaemia, granulocytopenia and thrombocytopenia. After treatment with blood transfusions and penicillin, and later injectable liver extract, folic acid and iron, a complete remission with normal regeneration of the bone marrow took

place. Two weeks later a fulminating myeloblastic leukeamia developed and a week later he died from internal haemorrhage after puncture of the spleen. Autopsy showed pronounced hepato-splenomegaly and universal myeloblastic infiltration.

2. A boy aged 14 developed acute myeloblastic leukaemia giving rise initially to neurological symptoms only: transitory paresis of the eye-muscles and paraesthesia corresponding to the trigeminal nerves. During treatment with urethane, liver extract and folic acid greater differentiation occurred in the bone marrow and in the peripheral blood; a decrease in the leukocyte count and a transitory clinical improvement were also noticed. Fifty days after the first appearance of the symptoms the patient died of heamorrhagic anaemia and sepsis.

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Communication re the Sixth International Congress of Pediatrics

The 6th International Congress of Pediatrics will be held at the end of July, 1950, in Zurich, Switzerland. President is Professor G. Fanconi, M. D.

Programme:

July 21st: Opening of the scientific and industrial exhibition. Opening of the public exhibition organized by the World Health Organization, the International Red Cross and the International Union for Child Welfare.

July 21st and 22nd: Advanced lectures, partly intended as introduction to the group lectures.

July 23rd (in the evening): Official reception.

July 24th, a.m.: First Plenary Session.

From July 24th, p.m. to July 27th: Group lectures of which 6–7 will be held simultaneously.

July 27th, p.m.: Excursion on the Lake of Zurich.

July 28th, a.m.: Second Plenary Session.

July 28th, p.m.: Group lecture held conjointly with the International Union against Venereal Disease.

July 28th (in the evening): Banquet.

July 28th and 29th: Advanced lectures.

July 31st (evening): Close of the exhibitions.

During the time of the Conference there will be demonstrations in and conducted tours through a number of laboratories, hospitals and welfare institutions in Zurich, further tours to historical places and to the "Village Pestalozzi", Trogen. Moreover a special programme for ladies will be arranged.

The date for registering the participation in the Congress has been deferred to *April 22nd, 1950*. Participants must register with the American Express Co. Inc., Sihlporteplatz 3, Zürich, or their agencies or correspondents in the different countries.

Each participant must be in possession of a Congress Card which is available at the agencies and correspondents of the American Express Co. Three different types of Congress Cards will be issued:

a) *Congress Card Serie "A", Sfr.100.–*, entitles the holder to participate in all sessions, visits and receptions, incl. the official reception of July 23rd, 1950, the official banquet and the excursion on the Lake of Zurich; further to free admission to the scientific and the industrial exhibition, receipt of all printed Congress literature (lecture volume, exhibition guide and official Congress programme).

b) *Congress Card Serie "B", Sfr.60.–*, for accompanying ladies, entitles the holder to participate in all sessions, visits and receptions, to free admission to the scientific and industrial exhibition, and to take part in the entertainments provided in the Ladies' Programme.

c) *Congress Card Serie "C", Sfr.60.–*, entitles the holder to participate in all scientific sessions, to free admission to the scientific and industrial exhibition and to receipt of all printed Congress literature.

Applications for hotel accomodation have to be made with the agencies or correspondents of the American Express Co. To colleagues who have to travel under restricted financial circumstances we can offer cheap lodging possibilities (price for lodging, breakfast and one meal Sfr.10.– per day), which are also available through the intermediary of the American Express Co.

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